IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re the application of:

Mika JOKINEN et al.

Serial Number: 09/913,643 Group Art Unit: 1618

Filed: October 19, 2001 Examiner: Fubara, Blessing M.

For: BIODEGRADABLE CERAMIC FIBRES FROM SILICA SOLS

APPEAL BRIEF TRANSMITTAL

Commissioner of Patents
P.O. Box 22313-1450
Alexandria, VA 22313

November 9, 2007

Sir:

Transmitted herewith is an Appeal Brief in this application.

A Petition and fee for an Extension of Time are also attached. It is not believed any additional fee is required for entry and consideration of this Appeal Brief. Nevertheless, the Commissioner is authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

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Enclosures:
Appeal Brief
Petition for Extension of Time

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REAL PARTY IN INTEREST

An assignment of the invention claimed in this application from the inventors to Bioxid Oy, a Finnish corporation, is recorded in the U.S. Patent and Trademark microfilm records at Reel 12434, Frame 0547. An assignment of the invention claimed in this application from Bioxid Oy to DelSiTech Oy, a Finnish corporation, is recorded at Reel 14638, Frame 810. Accordingly, the real party in interest is DelSiTech Oy.

RELATED APPEALS AND INTERFERENCES

There are no other prior or pending appeals, interferences or judicial proceedings known to Appellants, the Appellants' legal representative, or DelSiTech Oy which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 24-33 are pending, while claims 1-23 and 34 have been canceled. Each of pending claims 24-33 is being appealed from the rejections discussed below.

STATUS OF AMENDMENTS AFTER FINAL REJECTION

The Amendment After Final Rejection filed June 12, 2007 has been entered for purposes of appeal. No other amendments have been filed subsequent to the final rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

This appeal involves a rapidly-dissolving biodegradable silica fibre. Silica fibres are typically spun from a silica sol, which can be prepared by allowing a silica-alkoxide or an organically modified silicate to react with water in the presence of an acidic or basic catalyst. The functionality of the silica precursors and the degree of branching of the silica clusters formed affect the reaction and the spinnability of the resulting silica sol (Specification, page 1, lines 21-27 and page 6, lines 12-20).

Fibres can be spun from the silica sol using known techniques such as dry spinning and centrifugal spinning (page 6, line 21 to page 7, line 4), once the silica sol has reached a threshold viscosity value (Fig. 5). The silica sol is spinnable into a fibre within a certain time period rather than at a single point, and the viscosity of the sol increases during this time

period. Other factors which affect silica sol viscosity include the temperature of the sol and the amount of solvent present in the sol (page 5, lines 11-14).

The inventors have unexpectedly discovered the biodegradability of silica fibers can be varied - even when using the same recipe - by adjusting or controlling the viscosity of the spinning solution (page 5, lines 6-10). Fibers which are spun in the early stages of the spinnability period degrade more slowly in simulated body fluid that fibers spun in the later stages of spinnability. Fig. 8 shows the SiO_2 solubility of a silica fiber (FIB 1) in simulated body fluid as a function of silica sol viscosity at the starting point of the spinning process. Fiber solubility rate clearly increases as the starting viscosity increases. Compare, for example, fibers which were aged for 2 weeks after spinning. The "2 week fiber" whose starting point viscosity was 3.52 Pas has a lower solubility rate than the "2 week" fiber whose starting point viscosity was approximately 4 Pas. Similarly, the solubility rate of the 2 week fiber whose starting point viscosity was approximately 4 Pas is lower than the solubility rate of the 2 week fiber whose starting viscosity was 15 Pas.

Fibres spun from silica sols having a higher viscosity at lower temperature degrade more rapidly than the corresponding fibres spun at a higher temperature. See page 5, lines 18-24, page 11, lines 9-11, Example 5 and Table 3.

The claimed fiber has a solubility rate in simulated body fluid of 0.2 to 20 wt-%/h. The fiber will dissolve in about 21 days at its slowest solubility rate of 0.2 wt-%/hour.

In one embodiment, the claimed invention is a biodegradable silica fibre spun from silica sol, a biodegradation rate of the fibre being adjusted by controlling the starting point of the spinning process by a viscosity of the silica sol wherefrom the fibre is spun, the fibre having a solubility rate in simulated body fluid of 0.2 to 20 wt-%/h, preferably 0.2 to 8.5 wt-%/h (page 6, lines 5-11).

In a second embodiment, the claimed invention is a biodegradable silica fibre spun from a silica sol, a biodegradation rate of the fibre being adjusted by controlling the viscosity of the spinning sol wherefrom the fibre is spun, the fibre having a solubility rate in simulated body fluid of 0.2 to 20 wt-%/h, preferably 0.2 to 8.5 wt-%/h (page 6, lines 5-11).

The biodegradable fibre can be used as a delivery device or pharmaceutical preparation which is implanted, injected into or mucosally attached to a human or animal. A delivery device comprises the biodegradable fibre wherein the fibre contains a biologically active agent (page 7, lines 11-13). The biologically active agent can be a medicine, a protein, a hormone, a living or dead cell, a bacteria, a virus or a part thereof (page 8, line 1 to page 9, line 2).

A pharmaceutical preparation, such as a granulate or capsule, is a preparation which comprises the delivery device of the invention and possibly additional excipients useful in pharmaceutical preparations (page 7, lines 13-15).

In another embodiment, the present invention is a method for administering a biologically active agent to a human or animal such as a mammal, wherein the method comprises implanting, injecting or mucosally attaching a delivery device, where the delivery device comprises a biodegradable fibre comprising a biologically active agent, with the fibre spun from silica sol, a biodegradation rate of the fibre being adjusted by controlling the starting point of the spinning process by a viscosity of the silica sol wherefrom the fibre is spun, the fibre having a solubility rate in simulated body

fluid of 0.2 to 20 wt-%/h (page 3, lines 19-23; page 7, lines 5-10, and page 8, line 30).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Claims 24-33 stand finally rejected under 35 U.S.C. § 103(a) over PCT Patent Publication WO 97/45367 to Ahola et al. ("Ahola et al.").

2. Claims 24-33 stand finally rejected under 35 U.S.C. § 103(a) over German Patent DE 196 09 551 ("German '551").

ARGUMENT

As discussed above, a feature of claims 24-33 is a biodegradable silica fiber having a solubility rate in simulated body fluid of from 0.20 to 20 wt-%/hour. The fiber will completely dissolve in about 21 days at its slowest solubility rate.

A. AHOLA ET AL. FAILS TO RAISE A PRIMA FACIE CASE OF OBVIOUSNESS AGAINST CLAIMS 24-33

Ahola et al. discloses a controllably dissolvable silica xerogels prepared by a sol-gel process in which gelation of the sol and evaporation of solvent occur simultaneously by a spray drying method or by a fiber spinning or drawing technique (Page 3, lines 25-33). Example 2 illustrates the production of silica xerogel

fibers. Some of the fibers were kept at room temperature; others were heat treated at either 300° or 700° C. Some of the Ahola et al. fiber samples were placed in simulated body fluid or an aqueous solution within 48 hours of production; others were stored for 4 months prior to being placed in solution. Importantly, only the fibers kept at room temperature dissolved at any significant amounts. Room temperature fibers stored for 4 months in a dessicator dissolved 10 wt-% within 4 weeks (Ahola et al., page 14, lines 18-20). This 10 wt-%/4 week solubility rate corresponds to a solubility rate of 0.0148 wt-%/hour, which is significantly slower[1] than the 0.20 wt-%/hour minimum solubility rate of the claimed fiber.

Other Ahola et al. fiber samples were subcutaneously implanted into rats, and were examined after two weeks. Ahola et al. report that almost all fibers had integrated well into the surrounding connective tissue, no signs of resorption of the fibers could be observed by SEM examination, and that no Ca,P-layer could be observed on the surface of the fibers (Page 15, lines 14-17).

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[1]The undersigned previously argued the Ahola et al. fibers dissolve at a rate which is 20 times slower than the claimed fiber. However, the Ahola et al. fibers appear to dissolve at a rate which is about 13 times slower than the claimed fiber.

1. The Patent Office Concedes Ahola et al. Fails to Expressly Disclose the Solubility Rate Range Feature of the Claimed Fiber

The Patent Office concedes Ahola et al. does not disclose the solubility rate range of the claimed fiber (Page 10, line 12 of Official Action mailed February 12, 2007). Instead, the Patent Office argues the solubility rate of any fiber is an inherent characteristic of the fiber (Advisory Action, Continuation page, lines 1-2).

2. The Appellants Have Provided Data Demonstrating Fiber Solubility Rate Is Not Inherent to The Fiber

The solubility rate of a silica fiber is not inherent to the chemical composition of the fiber per se. See paragraph No. 9 of the Declaration Under 37 C.F.R. § 1.132 by Dr. Jokinen ("the Jokinen Declaration"). It is true solubility per se is an inherent property of a material, but the rate for reaching the solubility limit is not inherent. Thus, the rate of dissolution for two samples of chemically identical material in equal amounts in a dissolution medium such as water or simulated body fluid may be different due to a physical property such as pore structure. This can be observed for different forms of chemically identical sugar.

The same amount of powdered sugar will dissolve in coffee faster than a sugar cube.

Fig. 8 of Appellant's application contains data demonstrating that silica fiber solubility in simulated body fluid is not inherent to the fiber per se. Instead, the solubility rate of fibers prepared from the same recipe and aged for the same time (2 weeks) is shown to be dependent on the viscosity of the spinning sol at the starting point of the spinning process. Fibers which are spun in the early stages of the spinnability period degrade more slowly in simulated body fluid that fibers spun in the later stages of spinnability.

3. An Inherent Disclosure Ground for Rejection Cannot Replace an Express Disclosure

Ahola et al. *expressly* discloses a solubility rate (0.0148 wt-%/hour, which is significantly slower than the claimed solubility rate range) for its room temperature silica fibers which had been stored for four months. Ahola et al. *also* teaches that its other fibers did not dissolve in significant amounts. Given these express disclosures, it is improper for the Patent Office to argue Ahola et al. "inherently discloses" the claimed, more rapid, solubility rate range (0.20 to 20 wt-%/hour).

4. Ahola et al. Fails to Inherently Disclose The Solubility Range of the Claimed Fiber

Inherency may not be established by probabilities or possibilities, In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981). In this case, Example 2 of Ahola et al. provides a complete refutation of the Patent Office argument that the solubility rate of any fiber is an inherent characteristic of the fiber. As summarized above, samples of silica fibers prepared from the same recipe were subjected to various post-fiber production processing steps prior to *in vitro* solubility testing. Some of the fiber samples were heat treated, some were not. Some of the fiber samples were put into solution within 48 hours of production; other fiber samples were stored for 4 months prior to *in vitro* solubility testing.

Ahola et al. report that only silica fibers kept at room temperature dissolved at any significant amounts, and that the room temperature fibers stored for four months dissolved 10 w-% within 4 weeks. Thus, the silica fiber samples which had been heat treated did not dissolve in any significant amount. Yet if the solubility of these silica fiber samples was inherent to the fiber, all of the fiber samples should have exhibited the same *in vitro* solubility rate. See paragraph No. 10 of the Jokinen Declaration.

The Advisory Action contains several arguments in support of the Patent Office's "inherent disclosure" obviousness rejection. None of them have merit:

a. *In Vivo* Testing Does Not Inherently Disclose the Claimed Solubility Rate

The Patent Office cites *in vivo* testing of the Ahola et al. fiber samples in rats to justify its "inherent disclosure" argument. However, Ahola et al.'s statement that "Almost all the fibers had integrated well into the surrounding connective tissue" does not mean the fibers had dissolved. "Integration" refers to the state of being combined[2]; fiber dissolution would not lead to combination but instead to disintegration. Thus, fiber integration simply means the fibers mixed with the surrounding connective tissue. This is confirmed by Ahola et al.'s very next statement: "No signs of resorption of the fibers could be observed by SEM

[2]Integration - 1. The state of being combined, or the process of combining, into a complete and harmonious whole. 2. In physiology, the process of building up, as by accretion, anabolism, etc. 3. In mathematics, the process of ascertaining a function from its differential. 4. In molecular biology, a recombination event in which a genetic element is inserted. Stedman's Medical Dictionary 789 (25th ed. 1990)

examination." To "resorb" is to re-absorb[3]; there was no *in vivo* fiber re-absorption (dissolution) detected by Ahola et al.

b. Page 5, Lines 15-18 Fail to Inherently Disclose the Claimed Solubility Rate Range

Page 5, lines 15-18 of Ahola et al. disclose that fibers dissolve totally during the period desired when they are in contact with body fluid. This general statement does not specify the period during which fibers are in contact with body fluid. One of ordinary skill in the art has no way to calculate a solubility rate for the silica fibers from this disclosure; it does not inherently disclose or suggest a biodegradable silica fiber having a solubility rate in simulated body fluid of from 0.20 to 20 wt-%/hour.

c. Page 15, lines 12-15 Do Not Inherently Disclose the Claimed Solubility Rate Range

As discussed above, Ahola et al.'s *in vivo* testing of silica fibers in rats resulted in no silica fiber dissolution. Accordingly, this disclosure fails to "inherently" disclose or

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[3]Resorb - To re-absorb; to absorb what has been excreted, as an exudate or pus. Stedman's Medical Dictionary 1347 (25th ed. 1990). See also the discussion of resorbable vs. non-resorbable implants in German Patent DE 196 09 551, which is of record and discussed below.

suggest a biodegradable silica fiber having a solubility rate in simulated body fluid of from 0.20 to 20 wt-%/hour.

d. Example 5 Fails to Inherently Disclose The Claimed Solubility Rate Range

The claimed invention is a biodegradable silica fiber. Example 5 of Ahola et al. discloses the production of silica-xerogel discs, not fibers. Moreover, Example 5 expressly discloses that the silica-xerogel matrix dissolved "about 75 wt-% during 42 days". This dissolution rate is twice as long as the slowest solubility rate of the claimed fiber. Again, the Patent Office cannot substitute its inherent disclosure argument for the slower dissolution rate actually and expressly disclosed in Example 5 of Ahola et al.

e. No Additional Factual Showing Is Required

Fig. 8 of Appellants' application provides a factual showing that the solubility of a silica fiber in simulated body fluid is not determined just by its chemical composition or ageing period, but instead by the viscosity of the spinning solution at the point the fiber spinning process is begun. This factual showing undermines the basis of the Patent Office's inherent disclosure

ground for rejection. Ahola et al. teaches its fibers are either non-biodegradable or have solubility rates much slower than the claimed solubility range. In short, the Patent Office has no reasonable basis to require comparative data to demonstrate the Ahola et al. silica fiber does not possess the claimed solubility rate range of from 0.20 to 20 wt-%/hour.

5. The Claimed Fiber Is Nonobvious Over the Ahola et al. Fiber

35 U.S.C. § 103 forbids issuance of a patent when the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains, KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1734, 82 USPQ 1385 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art, and when present, secondary indicia of non-obviousness such as commercial success, long-felt but unsatisfied need, and failure of others, Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459 (1966).

There must be an apparent reason which would lead one of ordinary skill to modify or combine features of prior art references to establish obviousness of the claimed subject matter, KSR at 1741. Moreover, those of ordinary skill in the art must have a reasonable expectation of success in making the claimed composition or performing the claimed process. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). See Forest Lab., Inc. v. Ivax Pharm., Inc., 438 F.Supp.2d 479, 493-94, aff'd, 2007 U.S. App. LEXIS 21165, 84 USPQ2d 1099 (Fed. Cir. 2007)(Claim to enantiomer held nonobvious over its racemic mixture due to inability of those skilled in the art to resolve enantiomer; one of ordinary skill in the art seeking to resolve enantiomer would not have a reasonable expectation of success).

The prior art includes silica fibers prepared by a sol-gel process. Ahola et al. discloses silica fibers which have a slow solubility rate (0.0148 wt-%/hour) in simulated body fluid. In contrast, the claimed biodegradable silica fiber has a much faster solubility rate in simulated body fluid (0.20 to 20 wt-%/hour), and are prepared by adjusting or controlling the viscosity of the spinning sol.

The large difference in solubility rate between the prior art fiber of Ahola et al. and the claimed fiber renders the claimed fiber nonobvious. Ahola et al. does not disclose or suggest a rapidly-soluble fiber, much less that such a fiber can be prepared by manufacturing it during the later stages of sol spinnability. In this regard, it was known the viscosity of a sol increases over time, and that production problems relating to gelation of the sol can occur when fibers are spun from a late stage, high viscosity sol. See paragraph No. 14 of the Jokinen Declaration. Accordingly, those of ordinary skill in the art had no apparent reason to use a high viscosity sol and instead would be motivated not to use high viscosity silica spinning sols to manufacture fibers.

One of ordinary skill in the art would not have had a reasonable expectation he could modify the Ahola et al. fibers to achieve a silica fiber having a solubility rate in simulated body fluid of 0.20 to 20 wt-%/hour because fibers having such rapid solubility rates were unknown. See Paragraph No. 15 of the Jokinen Declaration. The inability of those of ordinary skill in the art to prepare such rapidly dissolving silica fibers demonstrates there

could not be a reasonable expectation of success, See Forest Lab. at 493-94.

B. THE FAST SOLUBILITY RATE OF THE CLAIMED FIBER IS SURPRISING AND UNEXPECTED

At the time of the invention, those of ordinary skill in the art employed similar manufacturing steps (except for controlling viscosity) to produce biodegradable silica fibers having relatively slow solubility rates. The speed at which the claimed biodegradable fiber dissolves in simulated body fluid would be surprising and unexpected because fibers with such fast solubility rates simply did not exist, and because those of ordinary skill in the art did not know how to make such fibers. See paragraph Nos. 15 and 16 of the Jokinen Declaration.

C. GERMAN '551 FAILS TO RAISE A PRIMA FACIE CASE OF OBVIOUSNESS AGAINST CLAIMS 24-33

As discussed above, a feature of claims 24-33 is a biodegradable silica fiber having a solubility rate in simulated body fluid of from 0.20 to 20 wt-%/hour. The fiber will completely dissolve in about 21 days at its slowest solubility rate.

1. German '551 Fails to Disclose the Solubility Range Feature of the Claimed Fiber

German '551 discloses a biodegradable silica fiber whose biodegradability is said to be controllable based upon its silanol content. Higher silanol content results in faster fiber degradation (English translation, page 5, lines 21-26). The fibers have a biodegradation rate of from 10 to 100 nm fibre radius/day. The silica fibers may have round, oval or bone-shaped cross-sections (page 4, lines 14-15) and a diameter of from 5 to 50 microns (page 4, lines 15-17).

a. German '551 Teaches Its 10 Micron Fiber Will Not Disintegrate for 50 Days

German '551 teaches that a fiber having a 10 micron diameter is completed degraded within 50 to 500 days (English translation, page 4, lines 21-25). In contrast, the claimed fiber will completely dissolve in about 21 days at its slowest solubility rate.

b. German '551 Does Not Disclose A Minimum Dissolution Time for its 5 Micron Diameter Fiber

German '551 does not disclose a corresponding biodegradation time range for a fiber having its minimum 5 micron diameter. Theoretically, such a fiber could degrade within 25 days, if one

assumed the fiber (1) has a round cross-section, (2) a 5 micron diameter, and (3) the maximum degradation rate of 100 nm fibre radius per day.

However, the combination of these assumptions is questionable in view of the entire disclosure of German '551. The same paragraph which discloses the fibre diameter range teaches the fibre may have a non-circular cross-section, and possess a cross-sectional surface area range of 100 to 500 μm^2. However, a fiber having a circular cross section and a 5 to 50 micron diameter range will have a cross section area of 19.6 μm^2 to 1,962 μm^2, not 100 to 500 μm^2. Similarly, the fibres produced in the German '551 Example had a diameter of from 5 to 30 microns and a cross-sectional surface area between 100 and 400 um^2. Again, a circular fiber having a 5 micron diameter has a cross section area of 19.6 μm^2. See Paragraph No. 5 of Dr. Jokinen's Supplemental Declaration ("Supplemental Declaration").

It is unknown whether the "fiber diameter" of German '551 refers to minimum fiber diameter, maximum fiber diameter or average fiber diameter. A 5 micron diameter fiber of German '551 may have a longer actual dissolution time than its theoretical dissolution time calculated based on a combination of assumptions, if the

minimum diameter values of German '551 refer to minimum diameters of a fiber having a non-circular cross-section. See Paragraph No. 6 of the Supplemental Declaration.

One of ordinary skill in the art would not interpret German '551 as suggesting a silica fiber having a solubility rate in simulated body fluid of from 0.20 to 20 wt-%/hour, particularly in view of its teachings regarding non-circular fibre cross-section and its values for fibre cross-sectional area.

2. Comparative Data Is Not Required to Show Non-obviousness Over German '551

The Patent Office argues comparative data must be presented to demonstrate the German '551 fibers do not possess the same solubility rate as the claimed fiber. However, this argument is based on the erroneous assumption the solubility rate of a silica fiber is based on its chemical composition per se. As demonstrated by Fig. 8 of the Appellants' application, silica fibers prepared from the same recipe exhibit different solubility rates based on the viscosity of the spinning solution at the point spinning of the fiber was begun.

The Patent Office must have a *sound* basis for believing the products of the prior art and the those of the applicant are the same before shifting the burden to the applicant to prove they are

not. See In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). In this case, there is no reason to assume the German '551 silica fibers have the same solubility rate as the claimed fiber. See Fig. 8 of the Appellant's application.

3. German '551 Leads One of Ordinary Skill Away From Producing the Claimed Fiber

When the prior art teaches away from combining or modifying known elements, the discovery of a successful way to modify to combine them is more likely to be nonobvious, KSR at 1740. German '551 teaches the higher the amount of silanol groups on the fiber, the higher is the fiber's degradation rate (English Translation, page 5, lines 1-4). Those of ordinary skill in the art know the number of silanol groups is reduced as the sol-gel reaction proceeds and also during the fiber spinning period. Thus, one of ordinary skill in the art, seeking to produce a rapidly dissolving silica fiber according to German '551, would begin spinning the fiber at the beginning of the fiber spinning period, when the spinning sol has a relatively low viscosity. In contrast, the Appellants have discovered rapidly-dissolving silica fibres can be produced from late stage, high viscosity spinning solutions (those with a relatively low silanol content). One of ordinary skill in the art would not be led to the claimed rapidly-dissolving silica

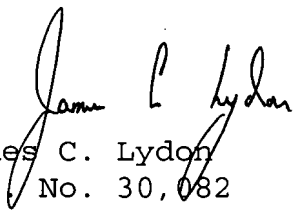
fiber because German '551 teaches away from its method of manufacture.

CONCLUSION

The Patent Office has erroneously assumed the solubility rate of a silica fiber is based solely on its chemical composition per se. The application contains experimental data demonstrating silica fiber solubility can be varied by changing the point at which fiber production begins based on the viscosity of the spinning solution from which the fiber is drawn. Neither Ahola et al. nor German '551 disclose or suggest the claimed, rapidly-dissolving silica fiber or how to make it. German '551 teaches away from the use of a high viscosity, low silanol content sol to spin a fiber having a fast solubility rate. Finally, those of ordinary skill in the art would consider a silica fiber having a solubility rate of from .20 to 20 wt-%/h to be unexpected and surprising in view of the state of the art just prior in time to the Appellant's invention.

Accordingly, this Board is respectfully requested to reverse the rejections of claims 24-33 and pass this application on to allowance.

Respectfully submitted,



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CLAIMS APPENDIX

Claims 24-33

24. (Previously presented) A delivery device comprising the biodegradable fibre according to claim 30, wherein the fibre contains a biologically active agent.

25. (Original) The delivery device according to claim 24, wherein said biologically active agent is a medicine, a protein, a hormone, a living or dead cell, a bacteria, a virus or a part thereof.

26. (Original) The delivery device according to claim 25, wherein said biologically active agent is a medicine.

27. (Previously presented) A pharmaceutical preparation comprising a delivery device according to claim 24.

28. (Previously presented) A method for administering a biologically active agent to a human or animal, wherein said method comprises implanting, injecting or mucosally attaching a delivery device, wherein said delivery device comprises a biodegradable

fibre according to claim 30 and wherein the fibre comprises a biologically active agent.

29. (Original) The method according to claim 28, wherein the biologically active agent is administered into a mammal.

30. (Previously presented) A biodegradable silica fibre spun from silica sol, a biodegradation rate of said fibre being adjusted by controlling the starting point of the spinning process by a viscosity of the silica sol wherefrom the fibre is spun, said fibre having a solubility rate in simulated body fluid of 0.2 to 20 wt-%/h.

31. (Previously presented) A biodegradable silica fibre according to claim 30, the solubility rate of the fibre in simulated body fluid being 0.2 to 8.5 wt-%/h.

32. (Previously presented) A biodegradable silica fibre spun from a silica sol, a biodegradation rate of the fibre being adjusted by controlling the viscosity of the spinning sol wherefrom

the fibre is spun, said fibre having a solubility rate in simulated body fluid of 0.2 to 20 wt-%/h.

33. (Previously presented) A biodegradable silica fibre according to claim 32, the solubility rate of the fibre in simulated body fluid being 0.2 to 8.5 wt-%/h.

EVIDENCE APPENDIX

1. Declaration Under 37 C.F.R. § 1.132 by Mika Jokinen.

This evidence was filed June 12, 2007 together with an Amendment After Final Rejection. The last paragraph of the continuation page of the Advisory Action mailed July 11, 2007 indicates the declaration was entered and considered by the Examiner.

2. Supplemental Declaration Under 37 C.F.R. § 1.132 by Mika Jokinen

This evidence was filed November 2, 2007. It is believed the supplemental declaration will be entered, as it clarifies paragraph No. 13 of the Jokinen Declaration.

3. English Translation of German Patent DE 196 09 551

This evidence was filed December 22, 2004. The Final Rejection mailed March 9, 2005 acknowledged receipt of the English translation.

4. WO 97/45367 to Ahola et al.

This evidence was filed as part of an Information Disclosure Statement on October 19, 2001. The Form PTO-1449 attached to the Official Action mailed April 8, 2003 indicates the Examiner considered this evidence.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Mika JOKINEN et al.

Serial Number: 09/913,643 Group Art Unit: 1618

Filed: October 19, 2001 Examiner: Fubara, Blessing M.

For: BIODEGRADABLE CERAMIC FIBRES FROM SILICA SOLS

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Mika Jokinen, declare and state:

1. I am the Research Director of DelSiTech Ltd., the owner of U.S. Patent Application S.N. 09/913,643 (hereinafter "this application").

2. I have been awarded various degrees in Chemical Engineering, including a Master of Science in 1993, a Licentiate of Technology in 1998 and a Doctor of Science in Technology in 1999. A copy of my resume is attached as Exhibit 1.

3. I am one of the inventors of the invention described and claimed in this application. Claims 24-33 are pending, and are directed to a biodegradable silica fibre spun from silica sol, the fibre having a solubility rate in simulated body fluid of 0.2 to 20 wt-%/h, and a delivery device, pharmaceutical preparation and a method for administering a biologically active agent to a human or animal, all based on the fibre.

4. The 0.2 to 20 wt-%/h solubility rate range of the claimed fiber means it dissolves very quickly in simulated body fluid - at the slowest solubility rate of 0.2 wt-%/hour, the claimed fiber will dissolve completely within 21 days.

5. The solubility rate of the claimed silica fiber in simulated body fluid is important because this *in vitro* property can be correlated with the fiber's dissolution rate achieved *in vivo* (biodegradability). It is important to understand that solubility measured as saturation level is not that important *in vivo* because the body liquid dissolved into (typically interstitial fluid) is constantly being renewed. Accordingly, saturation is most often not an issue.

6. I am aware claims 24-33 of this application have been rejected as obvious to one of ordinary skill in the art over PCT Patent Publication WO 97/45367 to Ahola et al. (hereinafter "Ahola et al.").

7. Example 2 of Ahola et al. reports that silica fibers spun from a sol were put into aqueous solution within 48 hours and also four months later. Additional fibers were treated at 300°C and 700°C in addition to the fibers kept at room temperature. These fibers were dissolved in either a tris-methylaminomethane HCl buffered aqueous solution or a simulated body fluid solution. Importantly, only fibers kept at room temperature dissolved in any significant amounts.

8. Ahola et al. report their room temperature fibers stored for four months dissolved by 10 wt-% within four weeks. These "room temperature" silica fibers had a

solubility rate in simulated body fluid of 0.0149 wt-%/hr, which is significantly less than the 0.2 to 20 wt-% solubility rate required by claims 24-33.

9. The Patent Office appears to argue the biodegradability of a silica fiber is inherent or based solely on its chemical composition (Official Action, page 12, last paragraph). However, the solubility rate of a silica fiber is not inherent to the chemical composition of the fiber per se. Instead, a silica fiber's solubility rate in simulated body fluid is determined, at least partly, by the specific processing parameters the fiber experiences during the spinning process.

10. Example 2 of Ahola et al. demonstrates that its silica fibers' solubility rate in simulated body fluid is not an inherent property, but is instead determined at least partially by processing parameters such as heat treatment. If solubility rate was an inherent property of silica fibers based only on chemical composition, then all of the fibers of Example 2 would have the same solubility rate. The factual showing of Example 2 of Ahola et al. demonstrates this is not the case - some of the Ahola et al. fibers dissolved and some (most) of them did not. Thus, their solubility rates were not the same.

11. I am aware claims 24-33 of this application have also been rejected as obvious to one of ordinary skill in the art over German Patent Publication 196 09 551 (hereinafter "German '551"). 12. The English language translation of German '551 discloses biologically degradable and/or biologically resorbable fibers and a method for their preparation in which the fibers are obtained by partial or complete

hydrolytic condensation of one or more hydrolytically condensable silicon compounds and/or precondensates derived therefrom. The hydrolytic precondensation is performed in water and eventually in the presence of a catalyst and/or a solvent and preferably according to a sol-gel method. The hydrolytic condensation produces a spinning mass from which continuous, long and/or short fibers can be prepared according to conventional methods.

13. The claimed fiber has a solubility rate in simulated body fluid of from 0.2 to 20 wt-%/hr. German '551 does not disclose or suggest this solubility rate range, which will result in complete fiber dissolution in about 21 days for the lower (slower) dissolution range limit. Instead, German '551 discloses a fiber whose fastest dissolution time is 50 days.

14. In my opinion, the prior art does not disclose or suggest a rapidly dissolvable silica fiber for at least two reasons. First, before the present invention it was not known the solubility rate of silica fibers would increase if the fibers were spun from sols of higher viscosities. Accordingly, there was no motivation or reason to spin fibers from sols having a high viscosity. Second, it was known that the viscosity of a silica sol increases over time, and that processing problems relating to gelation of the sol prior to completion of drawing of the fiber could be encountered when spinning fibers from sols of very high viscosities. Thus, those of ordinary skill in the art possessed a reason to avoid the use of high viscosity silica sols to spin fibers.

15. In my opinion, one of ordinary skill in the art would consider the fast solubility rate of the claimed fiber to be unexpected and surprising in view of both Ahola et al. and German '551. At the time of this invention, fibers with such fast solubility rates had not been achieved, despite the fact that the prior art employed much the same process steps (except for controlling the viscosity of the silica sol from which the fiber is spun). Accordingly, one of ordinary skill in the art would not have believed a biodegradable silica fiber could be made having a solubility rate in simulated body fluid such that the entire fiber would dissolve in less than 21 days.

16. In conclusion, I do not believe either Ahola et al. or German '551 raise a prima facie case of obviousness against the claimed silica fiber because neither reference suggests how to make a rapidly dissolvable silica fiber having a solubility rate in simulated body fluid of from 0.2 to 20 wt-%/hr. In my opinion, the speed at which the claimed fiber dissolves in simulated body fluid would be surprising and unexpected because fibers with such fast solubility rates simply did not exist, and because those of ordinary skill in the art did not know how to make such fibers.

17. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that further these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false

statements may jeopardize the validity of the application or any patent resulting therefrom.

Signed this 12. day of June, 2007.

By: _____
Mika Jokinen

Exhibit 1:
Resume of Dr. Mika Jokinen

Mika Jokinen, DSc
Research Director, Adjunct Professor

DelSiTech Ltd
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Tel.: 358 2 4788 643; 358 50 323 7603; telefax: 358 2 4788 120

PERSONAL INFORMATION

Mika Juhani Jokinen, b. 30th September 1965 (Turku, Finland)

EDUCATION, THESES & DEGREES

Master of Science in Technology (Chemical Engineering; Industrial Chemistry) Sept. 1993
Master's Thesis," Reactions of n-Butane on ZSM-5 Catalysts, Åbo Akademi University, Faculty of Chemical Engineering, Laboratory of Industrial Chemistry, 1993.

Licentiate of Technoloy (Chemical Engineering; Physical Chemistry) April 1998
Licentiate Thesis, "Colloidal Structures of Sol-Gel Derived Bioceramics", Åbo Akademi University, Department of Physical Chemistry, 1998.

Doctor of Science in Technology (Chemical Engineering; Physical Chemistry) June 1999
Doctoral Thesis, "Bioceramics by Sol-Gel Method: Processing and Properties of Monoliths, Films and Fibres", Åbo Akademi University, Department of Physical Chemistry, 1999.

Adjunct Professor (Medical Biomaterials), February 2003
Åbo Akademi University, Faculty of Chemical Engineering & Department of Physical Chemistry

WORKING EXPERIENCE & MAIN TASKS

CURRENT POSITIONS

- **DelSiTech Ltd since 1/2006**
  - **Research Director**

- **Åbo Akademi University since 2/2003**
  - **Adjunct Professor (Medical Biomaterials)**

EARLIER POSITIONS AT UNIVERSITIES

12/1992-06/1993& 09/1993-03/1994: Åbo Akademi University, Lab. of Industrial Chemistry
- **Research assistant** (development of nanoporous aluminium silicate-based catalysts (ZSM) for alkane and NO_x conversion) and hour-based teacher

04/1994-08/1999: Åbo Akademi University, Department of Physical Chemistry
- **Researcher** & PhD student (development of sol-gel derived SiO_2-& TiO_2-based biomaterials)

- 06/1999-12/2005: University of Turku, Department of Prosthetic Dentistry and Biomaterials Research & Turku Biomaterials Centre

- Research Scientist 06/1999 - 06/2000
- Senior Scientist 07/2000-12/2005

- Research on bioceramics (SiO_2, TiO_2, bioactive glass) & bioceramic-polymer composites for tissue repair applications, drug delivery and gene therapy
- Research instructor/supervisor for 5 PhD Students and 2 other postgraduate researchers:
  - Niko Moritz (11.11.2005), Marju Väkiparta (9.12.2005) and Reeta Viitala (16.12.2005) already defended their theses and received their PhD
- Research coordinator / responsible leader in several (>10) TEKES (National Technology and Innovation Agency of Finland)-funded, large interdisciplinary projects on biomaterials (bioceramics, polymer-bioceramic composites, drug & gene delivery)
- Member of a Center of Excellence Research Group (Academy of Finland): Bio- and Nanopolymers 01/2002-12/2005; bioactive composites of polymers and bioceramics & nanoscale modification of biomaterial surfaces

EARLIER POSITIONS IN COMPANIES & COMPANY-financed PROJECTS

Turun Eko-Vesi Oy (Ltd) 08/1994-02/1996:
- Part-time project engineer (water purification by electroflotation technique)

Bioxid Oy Ltd / DelSiTech Ltd: 03/2001-09/2002 + occasionally 9/2002-8/2004:
- Part-time Research Instructor (SiO_2-based biomaterials in delivery of biologically active agents (small drug molecules, proteins)

08/2004-12/2005 —Firm-financed project (DelSiTech Ltd), Turku Biomaterials Centre
- Part-time (25%) Research Instructor (SiO_2-based biomaterials in delivery of viruses for gene therapy & encapsulation of polymeric nanoparticles in SiO_2)

10/2005-12/2005 —Firm-financed project (StickTech Ltd), Turku Biomaterials Centre
- Hour-based consultation: evaluation of scientific results on fiber-reinforced composites for dental applications & recommendation for future actions

SCIENTIFIC PUBLICATION SUMMARY (updated June, 2007)

(Publications on silica & other (bio)ceramics, sol-gel technology and biomaterials):

- International papers with referee-practice (peer-reviewed): 25 published/in press, 1 submitted
- International Letter- & Proceedings -type publications: 13 published (9 full paper-refereed)
- Patents/ Patent Applications: 8
- Abstracts in International Conferences (35 of which 22 published as abstracts and 13 as proceedings papers as indicated above): 22

Subtotal: 69

- Other publications: 21 (abstracts/short papers in domestic seminars in Finland)

Total: 90

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Mika JOKINEN et al.

Serial Number: 09/913,643 Group Art Unit: 1618

Filed: October 19, 2001 Examiner: Fubara, Blessing M.

For: BIODEGRADABLE CERAMIC FIBRES FROM SILICA SOLS

SUPPLEMENTAL DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Mika Jokinen, declare and state:

1. I executed a Declaration Under 37 C.F.R. § 1.132 for this application on June 12, 2007 ("the Jokinen Declaration"). A copy of the Jokinen Declaration is attached as Exhibit 1.

2. Paragraph No. 13 of the Jokinen Declaration correctly describes German Patent Publication 196 09 551 ("German '551") as disclosing a fiber whose fastest dissolution time is 50 days. See page 4, lines 24-55 of the English translation of German '551 ("A fibre according to the invention having a diameter of 10 µm is thus completely degraded within 50-500 days".)

3. German '551 also states its fibres have degradation rates between 10 and 100 nm fibre radius per day, with the degradation rate correlating with the amount of silanol groups of the fibre

(English translation, page 4, lines 21-24). The German '551 fibers may have round, oval or bone-shaped cross-sections (English translation, page 14-15), and a diameter of between 5 and 50 μm (English translation, page 4, lines 15-17).

4. German '551 does not disclose a degradation rate or range for fibres having a 5 micron diameter. It is possible to calculate a maximum degradation rate of 25 days, but only if one assumes the fibre (1) has a round cross-section, (2) a 5 micron diameter, and (3) the maximum degradation rate of 100 nm fibre radius per day.

5. In my opinion, one of ordinary skill in the art would consider the combination of these assumptions to be speculative, and would not consider German '551 to disclose silica fibres having a 25 day minimum dissolution time. Instead, one of ordinary skill in the art would view its mention of a 5 micron diameter fibre in the context of the entire German '551 disclosure. The same paragraph which discloses a fibre diameter range teaches the fibre may have a non-circular cross-section, and possess a cross-sectional surface area range of 100 to 500 μm^2. However, a fiber having a circular cross section and a 5 to 50 micron diameter range will have a circular cross section of 19.6 μm^2 to 1,962 μm^2. This disparity between the cross-sectional area range of the German '551 fiber and the cross-sectional area of a corresponding circular fiber is also present in the German '551 example, which is said to

have produced fibers having a diameter of from 5 to 30 microns and a cross-sectional surface area between 100 and 400 um^2 (English translation, page 9, lines 16-18).

6. German '551 mentions its fibre degradation rate range in a separate paragraph subsequent to its discussion of non-uniform fiber cross-section and fiber diameter. It is unknown whether the "fiber diameter" of German '551 refers to minimum fiber diameter, maximum fiber diameter or average fiber diameter. The German '551 fiber may have a longer actual dissolution time than one calculated using the assumption of a circular fiber cross-section, if the minimum values mentioned in German '551 refer to the minimum diameters of non-circular cross-section fibers.

7. I have reviewed the Jokinen Declaration, and affirm all of my statements therein, including those of Paragraph No. 13 as supplemented above.

8. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that further these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false

statements may jeopardize the validity of the application or any patent resulting therefrom.

By: _____
Mika Jokinen

Signed this 24th day of October, 2007.

Exhibit 1:
Declaration Under 37 C.F.R. § 1.132

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Mika JOKINEN et al.

Serial Number: 09/913,643 Group Art Unit: 1618

Filed: October 19, 2001 Examiner: Fubara, Blessing M.

For: BIODEGRADABLE CERAMIC FIBRES FROM SILICA SOLS

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Mika Jokinen, declare and state:

1. I am the Research Director of DelSiTech Ltd., the owner of U.S. Patent Application S.N. 09/913,643 (hereinafter "this application").

2. I have been awarded various degrees in Chemical Engineering, including a Master of Science in 1993, a Licentiate of Technology in 1998 and a Doctor of Science in Technology in 1999. A copy of my resume is attached as Exhibit 1.

3. I am one of the inventors of the invention described and claimed in this application. Claims 24-33 are pending, and are directed to a biodegradable silica fibre spun from silica sol, the fibre having a solubility rate in simulated body fluid of 0.2 to 20 wt-%/h, and a delivery device, pharmaceutical preparation and a method for administering a biologically active agent to a human or animal, all based on the fibre.

4. The 0.2 to 20 wt-%/h solubility rate range of the claimed fiber means it dissolves very quickly in simulated body fluid - at the slowest solubility rate of 0.2 wt-%/hour, the claimed fiber will dissolve completely within 21 days.

5. The solubility rate of the claimed silica fiber in simulated body fluid is important because this *in vitro* property can be correlated with the fiber's dissolution rate achieved *in vivo* (biodegradability). It is important to understand that solubility measured as saturation level is not that important *in vivo* because the body liquid dissolved into (typically interstitial fluid) is constantly being renewed. Accordingly, saturation is most often not an issue.

6. I am aware claims 24-33 of this application have been rejected as obvious to one of ordinary skill in the art over PCT Patent Publication WO 97/45367 to Ahola et al. (hereinafter "Ahola et al.").

7. Example 2 of Ahola et al. reports that silica fibers spun from a sol were put into aqueous solution within 48 hours and also four months later. Additional fibers were treated at 300°C and 700°C in addition to the fibers kept at room temperature. These fibers were dissolved in either a tris-methylaminomethane HCl buffered aqueous solution or a simulated body fluid solution. Importantly, only fibers kept at room temperature dissolved in any significant amounts.

8. Ahola et al. report their room temperature fibers stored for four months dissolved by 10 wt-% within four weeks. These "room temperature" silica fibers had a

solubility rate in simulated body fluid of 0.0149 wt-%/hr, which is significantly less than the 0.2 to 20 wt-% solubility rate required by claims 24-33.

9. The Patent Office appears to argue the biodegradability of a silica fiber is inherent or based solely on its chemical composition (Official Action, page 12, last paragraph). However, the solubility rate of a silica fiber is not inherent to the chemical composition of the fiber per se. Instead, a silica fiber's solubility rate in simulated body fluid is determined, at least partly, by the specific processing parameters the fiber experiences during the spinning process.

10. Example 2 of Ahola et al. demonstrates that its silica fibers' solubility rate in simulated body fluid is not an inherent property, but is instead determined at least partially by processing parameters such as heat treatment. If solubility rate was an inherent property of silica fibers based only on chemical composition, then all of the fibers of Example 2 would have the same solubility rate. The factual showing of Example 2 of Ahola et al. demonstrates this is not the case - some of the Ahola et al. fibers dissolved and some (most) of them did not. Thus, their solubility rates were not the same.

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hydrolytic condensation of one or more hydrolytically condensable silicon compounds and/or precondensates derived therefrom. The hydrolytic precondensation is performed in water and eventually in the presence of a catalyst and/or a solvent and preferably according to a sol-gel method. The hydrolytic condensation produces a spinning mass from which continuous, long and/or short fibers can be prepared according to conventional methods.

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14. In my opinion, the prior art does not disclose or suggest a rapidly dissolvable silica fiber for at least two reasons. First, before the present invention it was not known the solubility rate of silica fibers would increase if the fibers were spun from sols of higher viscosities. Accordingly, there was no motivation or reason to spin fibers from sols having a high viscosity. Second, it was known that the viscosity of a silica sol increases over time, and that processing problems relating to gelation of the sol prior to completion of drawing of the fiber could be encountered when spinning fibers from sols of very high viscosities. Thus, those of ordinary skill in the art possessed a reason to avoid the use of high viscosity silica sols to spin fibers.

15. In my opinion, one of ordinary skill in the art would consider the fast solubility rate of the claimed fiber to be unexpected and surprising in view of both Ahola et al. and German '551. At the time of this invention, fibers with such fast solubility rates had not been achieved, despite the fact that the prior art employed much the same process steps (except for controlling the viscosity of the silica sol from which the fiber is spun). Accordingly, one of ordinary skill in the art would not have believed a biodegradable silica fiber could be made having a solubility rate in simulated body fluid such that the entire fiber would dissolve in less than 21 days.

16. In conclusion, I do not believe either Ahola et al. or German '551 raise a prima facie case of obviousness against the claimed silica fiber because neither reference suggests how to make a rapidly dissolvable silica fiber having a solubility rate in simulated body fluid of from 0.2 to 20 wt-%/hr. In my opinion, the speed at which the claimed fiber dissolves in simulated body fluid would be surprising and unexpected because fibers with such fast solubility rates simply did not exist, and because those of ordinary skill in the art did not know how to make such fibers.

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Signed this 12. day of June, 2007.

By: _____
Mika Jokinen

Exhibit 1:
Resume of Dr. Mika Jokinen

Mika Jokinen, DSc
Research Director, Adjunct Professor

DelSiTech Ltd
Itäinen Pitkäkatu 4 B
FIN-20520 Turku, FINLAND
E-Mail: mika.jokinen@delsitech.com
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PERSONAL INFORMATION

Mika Juhani Jokinen, b. 30th September 1965 (Turku, Finland)

EDUCATION, THESES & DEGREES

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WORKING EXPERIENCE & MAIN TASKS

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- **Åbo Akademi University since 2/2003**
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- Researcher & PhD student (development of sol-gel derived SiO_2-& TiO_2-based biomaterials)

- 06/1999-12/2005: University of Turku, Department of Prosthetic Dentistry and Biomaterials Research & Turku Biomaterials Centre

- Research Scientist 06/1999 - 06/2000
- Senior Scientist 07/2000-12/2005

- Research on bioceramics (SiO_2, TiO_2, bioactive glass) & bioceramic-polymer composites for tissue repair applications, drug delivery and gene therapy
- Research instructor/supervisor for 5 PhD Students and 2 other postgraduate researchers:
  - Niko Moritz (11.11.2005), Marju Väkiparta (9.12.2005) and Reeta Viitala (16.12.2005) already defended their theses and received their PhD
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- Member of a Center of Excellence Research Group (Academy of Finland): Bio- and Nanopolymers 01/2002-12/2005; bioactive composites of polymers and bioceramics & nanoscale modification of biomaterial surfaces

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Bioxid Oy Ltd / DelSiTech Ltd: 03/2001-09/2002 + occasionally 9/2002-8/2004:
- Part-time Research Instructor (SiO_2-based biomaterials in delivery of biologically active agents (small drug molecules, proteins)

08/2004-12/2005 —Firm-financed project (DelSiTech Ltd), Turku Biomaterials Centre
- Part-time (25%) Research Instructor (SiO_2-based biomaterials in delivery of viruses for gene therapy & encapsulation of polymeric nanoparticles in SiO_2)

10/2005-12/2005 —Firm-financed project (StickTech Ltd), Turku Biomaterials Centre
- Hour-based consultation: evaluation of scientific results on fiber-reinforced composites for dental applications & recommendation for future actions

SCIENTIFIC PUBLICATION SUMMARY (updated June, 2007)

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- Abstracts in International Conferences (35 of which 22 published as abstracts and 13 as proceedings papers as indicated above): 22

Subtotal: 69

- Other publications: 21 (abstracts/short papers in domestic seminars in Finland)

Total: 90

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Mika JOKINEN et al.

Serial Number: 09/913,643 Group Art Unit: 1615

Filed: October 19, 2001 Examiner: Fubara, Blessing M.

For: BIODEGRADABLE CERAMIC FIBRES FROM SILICA SOLS

TRANSLATOR'S DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, the undersigned, hereby declare as follows:

1. that I am familiar with the German and English languages;

2. that I authored the attached translation;

3. that to the best of my knowledge and belief, the attached is a true and complete translation of German Patent 196 09 551; and

4. that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the United States Code and that such willful false

statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

By: Satu Kuorikoski
Signature

Satu Kuorikoski
Typed Name

Date: December 21, 2004

Abstract

Biodegradable and/or biologically resorbable (continuous) fibres, a method for their preparation and their use as reinforcement fibres

The invention relates to biologically degradable and/or biologically resorbable (continuous) fibres and a method for their preparation. The (continuous) fibres are obtained by partial or complete hydrolytic condensation of one or more hydrolytically condensable silicon compounds and/or precondensates derived therefrom. The hydrolytic condensation is performed under the effect of water and eventually in the presence of a catalyst and/or a solvent and preferably according to a sol-gel-method. With this partial or complete hydrolytic condensation is obtained a spinning mass, which can be processed to continuous and/or long and/or short fibres by conventional methods.

Description

The invention relates to biologically degradable and/or biologically resorbable (continuous) fibres, a method for their preparation and their use as reinforcement fibres.

Organic polymer fibres are used as fibre material in human tissue (US 3,297,033; L. Fambri, A. Pegoretti, M. Mazzurana, C. Migliaresi, J. Mat. Sci.: Materials in Medicine, 5, 1994, 679; P. Ylinen, J. Mat. Sci.: Materials in Medicine, 5, 1994, 522; D. G. Tunc, Clinical Materials 8, 1991, 119; R. A. Olson, D. L. Roberts, D. B. Osbon, Oral. Surg., 53, 1982, 441; J. W. Leenslag, M. T. Kroes, A. J. Pennings, B. Van Cer Lei, New Polym. Mater., 1, 1988, 111; C. M. Agraval, K. F. Haas, D. A. Leopold, H. G. Clark, Biomaterials, 13, 1992, 176; D. H. Lewis in: Biodegradable polymers as drug delivery systems, eds. M. Chasin, R. Langer, Marcel Dekker, New York, 1990, 1; S. H. Hyon, K. Jamshidi, Y. Ikada in Polymers as biomaterials, eds. S. Shalaby, A. S. Hoffmann, B. D. Ratner, T. A. Horbett, Plenum Press, New York, 1984, 51).

However, biologically degradable and/or resorbable materials, that can be used e.g. in surgery, are wanted in the medical technique for fixing eventually broken bones in the human body until the fracture is healed. For fixing are used for example screws, that are prepared of biologically degradable and/or biologically resorbable organic polymers. Their big

advantage compared to traditional metal screws is e.g. the resorbability in the human body after the occurred healing, which usually takes couple of months. Through the resorption of the implant second operations for removing the introduced material are not necessary any more.

Unfortunately, the biologically degradable osteosynthesis materials according to the prior art, that consist e.g. of lactid acid derivatives (polylactides) have, however, a weighty disadvantage. Their mechanical strength is, compared to metal materials, not so high. It is to be expected, that the introduction of reinforcement fibres to the compact material can substantially improve its mechanical strength. However, it is necessary, that the fibres degrade under conditions prevailing in the human organism as fast or as slow, as the polylactide material itself.

According to the prior art unresorbable carbon fibres are used in the preparation of binding materials and for their reinforcement. Such materials are used e.g. for fixations of cords or ligaments. The disadvantage is, however, that the foreign substance, which can cause infections and other negative reactions, remains in the organism.

Metal implants differ in their mechanical characteristics strongly from those of the body tissue and have therefore an additional disadvantage. Metals are substantially stronger than natural bones. This leads in the immediate environment of the metal implant to resorption of bone substance with the result, that the implant loosens. It would be advantageous, if materials would be available, that conform in their mechanical properties with those of the tissue.

Steve T. Lin et al. describe in Biomaterials 1994, Vol. 15 No. 13, p 1057 – 1061, biologically absorbable fibres of calcium-iron-phosphate-glasses. They are, however, manufactured by a very energy-intensive and costly melting process.

From DE 29009991 C2 are known silicic acids fibres, which can also be used as reinforcement fibres in fibre bonding materials. The fibres described therein are obtained by handling the water glass fibres with acids or saline solutions, through which the resulting fibres do not contain any additional substances besides SiO_2 and smallish amounts of wa-

ter with the result, that these fibres have only an extremely low degradation rate and can therefore not be used as resorbable material.

DE 3510753 C2 discloses high temperature silicon dioxide fibre material, which is obtained by dry spinning of water glass and by succeeding dehydration and by one hour tempering at 1500°C. This fibre material has a very high SiO_2 content of more than 95 percentage by weight, a density between 1.9 and 2.4 g/cm^3 and a content of microcrystalline cristobalite areas from 5% to 10%. These fibres show likewise very slow degradation rates in body-like medias and additionally tissue reactions to the crystalline areas are to be expected, which is not allowed when used in medical technology.

The aim of the present invention is now to prepare biologically degradable and/or biologically resorbable (continuous) fibres, which can be used e.g. as reinforcement fibres for biologically degradable and/or biologically resorbable (implant) materials. The toxicological properties and the biological compatibility of these fibres should be adjustable corresponding to each purpose of use, so that these fibres can also be used in human medicine, if required. Additionally, the resorbability of the fibres should be controllable and adjustable to the requirements of each purpose of use. Thus, there are e.g. different requirements for degradation rates of implants made of binding materials for fast healing tissue and for slow occurring healing processes. The fibres should be suitable for preparation of biologically degradable binding materials, they should be especially usable as reinforcement components in polymers, e.g. polylactide. These binding materials should then be mouldable to screws, plates, bands or sewing material. The fibres should be able to replace carbon fibres and be suitable for preparation of implants (e.g. cords or ligaments), which are fully resorbable in human organism, so that after the resorption there is no foreign substance, that can cause infections or other negative reactions, left in the organism. Additionally, the fibres should be such that the mechanical properties of the binding materials can be adjusted through fibres to those of the tissue in the human organism. The fibres should not only be usable as reinforcement components in binding materials, but also as surgical sewing material.

The aim of the present invention is further to obtain a method, by which biologically degradable and/or biologically resorbable fibres (continuous an/or short fibres) having the above-mentioned properties can be prepared. The method must be devised so, that as a

result fibres having defined mechanical characteristic values are obtained and that continuous as well as long or short fibres can be prepared. The method should further be so variable, that the toxicological properties, the resorbability and the degradation rate of the fibres can be adjusted to the requirements of each purpose of use. Further, the method should not be energy-intensive or costly.

This aim is obtained through (continuous) fibres, which are attained by partial or complete hydrolytic condensation of one or more condensable silica compounds and/or precondensates derived therefrom. The hydrolytic condensation is performed by action of water and eventually in the presence of a catalyst and/or a solvent and preferably according to a sol-gel method.

By this partial or complete hydrolytic condensation a spinning mass is obtained, which is mouldable according to conventional methods to continuous and/or long and/or short fibres.

The fibres according to the invention show, depending on the initial mixture for the spinning mass, round, oval or bone-shaped forms of cross-section. The diameters of the fibres according to the invention are, depending on the spinning conditions, between 5 and 50 µm, preferably between 10 and 20 µm. The cross-section surfaces show values between 100 and 500 μm^2, preferably between 150 and 250 μm^2. The fibres according to the invention have tensile strengths of 100 - 800 MPa and E-modules of 15 GPa. The average ultimate elongation of the fibres according to the invention is at circa 2%.

It was unexpectedly found out that the fibres according to the invention are biologically degradable and biologically resorbable and dissolve in weakly basic, body-like fluids having degradation rates between 10 and 100 nm fibre radius per day, whereby the degradation rate correlates with the amount of silanol groups of the fibre. A fibre according to the invention having a diameter of 10 µm is thus completely degraded within 50 – 500 days.

After the complete hydrolysis of the spinning mass the fibres according to the invention have a formal chemical composition $Si_n(OH)_{2x}O_{2n-x}$. With the degree or extent of the condensation (polycondensation), i.e. with the amount of the remaining silanol groups the degradation rate and the resorbability of the fibres according to the invention can be controlled

intentionally and adjusted to the requirements of the application in question. The smaller is the extent of the condensation, i.e. the higher is the amount of the remaining OH-groups, the higher is the degradation rate and the higher is the resorbability of the fibres according to the invention.

The fibres according to the invention can be used for preparation of biologically degradable and /or biologically resorbable binding materials, whereby they are introduced e.g. as reinforcement components to biologically degradable and/or resorbable polymers, e.g. to polylactide, polyglycolide, hydroxyapatite, polyesteramide, starch, BIOCELLAT®, polydioxanone, PDS, GELFILM®, Biofix®, TCP, DXO, polyglactin, PLA/PG copolymer or Ca-phosphate. These binding materials produced in this way can be moulded to e.g. screws, plates or bands. Through the combination of biologically degradable, inorganic fibres with biologically degradable polymers biologically degradable materials are prepared, which in their mechanical properties overcome clearly those of the pure polymer compact materials. Herewith is prevented a premature mechanical interference of biologically degradable implants. The fibres according to the invention can substitute carbon fibres, which are used e.g. for repairing of ligaments and bands. For the substitution of the unresorbable carbon fibres with the fibres according to the invention materials for implants (e.g. for ligaments and bands) are now available, which are completely resorbable in the human organism. No foreign substance, which can cause infections or other negative reactions, remains in the organism.

Through the silanol content of the fibres according to the invention their degradation rate and their resorbability can be affected intentionally and thus adjusted to the requirements of the application purpose in question. In case of fast curing tissue, for example, a higher degradation rate of the implanted composite material as in case of more slowly occurring healing processes has to be aimed at. Accordingly, fibres according to the invention have higher silanol content for fast resorbing implants as for those to be resorbed slowly.

The mechanical properties of the fibres according to the invention can also be controlled intentionally through the degree of the hydrolysis and be adjusted to the requirements of each purpose of use. If, for the preparation of the fibres according to the invention silica compounds are used, which have in their molecule at least one organic, hydrolysable

group (e.g. – OC_2H_5), then in the incomplete hydrolysis C_2H_5O groups remain in the fibre, which influence their mechanical properties.

The fibres according to the invention can also be directly used as surgical sewing material. It is also possible to use the fibres according to the invention for preparation of the depots for active agent, whereby the active agents are released gradually during fibre degradation. It is also possible to change the texture of the implants with the aid of the fibres according to the invention so, that the formation of collagen is stimulated through the fibrous surface, so that a stable biological surface is formed on the surface of the implant thus improving its biocompatibility.

The preparation of the spinning mass, i.e. the hydrolytic condensation of the hydrolysable silica compounds is performed preferably through a sol-gel method, as disclosed for example in DE-A1 27 58 414, 27 58 415, 30 11 761, 38 26 715 and 38 35 968. In most cases the hydrolytic condensation can occur in that to the silica compounds to be hydrolysed, which are either as such or as dissolved in a suitable solvent, is directly added the necessary water at the room temperature or under light cooling – preferably by mixing and in the presence of a hydrolysis or condensation catalyst – and in that the resulting mixture is after that mixed for a while (from one to several hours).

For the preparation of spinning mass are preferably used silica compounds of the general formula I,

SiX_4 (I)

in which rests X are the same or different and stand for hydroxy, hydrogen, halogen, amino, alkoxy, acyloxy, alkyl carbonyl or alkoxy carbonyl and derive from alkyl rests, which are eventually substituted straight-chain, branched or cyclic rests having 1 to 20 carbon atoms, especially having 1 to 10 carbon atoms and preferably lower alkyl rests having 1 to 6 carbon atoms, and can be interrupted by oxygen or sulphur atoms or by amino groups. Particular examples are methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl, cyclohexyl, 2-ethylhexyl, dodecyl and octadecyl.

It is likewise possible to use mixtures of silica compounds of the formula I, precondensates derived therefrom or mixtures of monomers and precondensates.

Silans of the formula I are commercially purchaseable or preparable according to the methods as described for example in "Chemie und Technologie der Silicone" (W. Noll, Verlag Chemie, Weinheim, 1968). Without restricting generality concrete examples for compounds of formula I are:

$Si(OMe)_4$, $Si(OMe)_3(OEt)$, $Si(OMe)_2(OEt)_2$, $Si(OMe)(OEt)_3$, $Si(OEt)_4$, $Si(O\text{-}i\text{-}Pr)_4$, $Si(OMe)_3(O\text{-}i\text{-}Pr)$, $Si(OMe)_2(O\text{-}i\text{-}Pr)_2$, $Si(OMe)(O\text{-}i\text{-}Pr)_3$, $Si(OEt)_3(O\text{-}i\text{-}Pr)$, $Si(OEt)_2(O\text{-}i\text{-}Pr)_2$, $Si(OEt)(O\text{-}i\text{-}Pr)_3$, $Si(O\text{-}n\text{-}Pr)_4$, $Si(OMe)_3(O\text{-}n\text{-}Pr)$, $Si(OMe)_2(O\text{-}n\text{-}Pr)_2$, $Si(OMe)(O\text{-}n\text{-}Pr)_3$, $Si(OEt)_3(O\text{-}n\text{-}Pr)$, $Si(OEt)_2(O\text{-}n\text{-}Pr)_2$, $Si(OEt)(O\text{-}n\text{-}Pr)_3$, $Si(O\text{-}i\text{-}Pr)_3(O\text{-}n\text{-}Pr)$, $Si(O\text{-}i\text{-}Pr)_2(O\text{-}n\text{-}Pr)_2$, $Si(O\text{-}i\text{-}Pr)(O\text{-}n\text{-}Pr)_3$, $Si(OMe)(OEt)_2(O\text{-}i\text{-}Pr)$, $Si(OMe)(OEt)_2(O\text{-}n\text{-}Pr)$, $Si(OMe)(OEt)(O\text{-}i\text{-}Pr)_2$, $Si(OMe)(O\text{-}n\text{-}Pr)_2$, $Si(OMe)(O\text{-}i\text{-}Pr)(O\text{-}n\text{-}Pr)_2$,

With preferable embodiments for preparation of the spinning mass such a big amount of water is used for the hydrolysis, that the molar ratio of $SiX_4 : H_2O$ is between 1 : 1 and 1 : 10, preferably between : 1.5 and 1 : 2.5.

If no phase-transfer catalyst is used, preferably a water-soluble solvent (S) or a solvent mixture is used for the preparation of the spinning mass, so that the silica compound(s) and water form a homogenous phase. Without restricting generality examples for suitable solvents are methanol, ethanol, n-propanol, and i-propanol. Mixtures are also possible. It is especially preferable, if the molar ratio $S : SiX_4$ is at least 1 : 1. If a phase-transfer catalyst is used, the presence of a water-soluble solvent is not absolutely necessary.

For other preferable embodiments for the preparation of the spinning mass the mixture of hydrolysable silica compound, water-soluble solvent, water and catalyst is mixed until a dynamic balance has been adjusted and the hydrolysis has then quasi ended.

Additionally, it is preferable, if for the preparation of the spinning mass, after the ended hydrolysis, solvent is taken away from the resulting mixture until the remaining mixture has in room temperature and in shear rate of 20 s^{-1} a viscosity between 0,05 and 50 Pa ·s, preferably between 0,5 and Pa·s.

For the preparation of especially homogenous fibres it is preferable, if the spinning mass is exposed to a further filtration before the spinning process.

For the preparation of high-quality continuous fibres of the invention having a flat fibre surface the following procedure for the preparation of the spinning mass has turned out to be particularly preferable. A spinning mass is prepared by hydrolytic (partial) condensation of one or more silica compounds of the general formula I and /or of precondensates derived therefrom by adding water and eventually in the presence of a catalyst, whereby such a big amount of water is used, that the molar ratio $SiX_4 : H_2O$ is between 1 : 1 and 1 : 10, preferably between 1 : 1 and 1 :1,5. Such a big amount of a water-soluble solvent (S) or a mixture of solvents is used, that the molar ratio is $S : SiX_4 \geq 1$. After the terminated hydrolysis and the adjustment of a dynamic balance the S is taken away until the resulting mixture has in room temperature and in shear rate of 20 s^{-1} a viscosity between 0,05 and 50 Pa·s. After the removal of the solvent or the mixture of solvent the resulting mixture is exposed to filtration. It is preferable, if the viscosity is between 0,5 and 3 Pa·s or if the mesh size of the filtration medium is 0,5 to 1,5 mm. It is especially preferable, if the filtration medium has a mesh size of 1 mm. After the filtration the resulting mixture is allowed to stand until it obtains spinnability. Depending on the temperature the ripening time is between several hours (e.g. 6 hours) and several months and is determined by the residual content of the solvent or mixture of solvent. After the termination of the ripening time a homogenous, readily mouldable spinning mass is obtained, which remains stable and thus spinnable for a while (from 30 minutes to some hours), before it gelates. The spinning mass is moulded to threads, which are also eventually dried.

In this way particularly homogenous continuous fibres are obtained.

The fibres prepared in this way can also comprise hydrolysable groups X, which, if they are not desired, disappear in the course of time when stored in room temperature. This can be IR-spectroscopically observed.

The preparation of the fibres of the invention is described more detailed by means of an exemplary embodiment.

Example

The educts TEOS (tetraetoxysilane), EtOH, H_2O ja HNO_3 are mixed in the molar ratio of 1 : 1,26 : x : 0.01 (with x = 1,6, 1,7, 1,8, 1,9 and 2,0) and stirred intensively 5 hours in room temperature. The resulting solvents are placed in open dishes in a water bath warmed up to 70° C, wherein they remain until to a defined weight loss. After that it is cooled and filtered through a refined steel net having a mesh size of 1 mm x 1 mm. The filtrate is subjected to an aging time of from 6 hours to 6 moths depending on the weight loss in a closed dish at a temperature of 3°C. The resulting spinning mass is very homogeneous and stable and spinnable for some time.

The preparation of fibres is performed in a dry-spinning device. The spinning mass is filled into a spinning head cooled to –15°C under a pressure of 10 – 15 bar first through a refined steel net having a mesh size of 80 µm 20 x 80 µm and then pressed through the nozzle having a diameter of 100 µm.

The resulting continuous thread is wrapped after a drying path of 1 m on a rotating cylinder.

The resulting fibres show, depending on the initial mixture, i.e. on the amount of water added, round, oval or bone-shaped cross-section forms having diameters between 5 and 30 µm. The cross-section surfaces are between 100 and 400 μm^2. The fibre surface is flat and has no wave profile in any case. The tensile strength measurements of the fibres gave values of 100 – 800 Mpa.

IR-spectra made of fibre material show a Si – OH -bond at 950 cm^{-1} and C – H signals at 3000 cm^{-1}. Also a partially hydrolysed and partially condensated etoxy-silanol-fibre is at hand. After circa 2 months storage in room temperature no more C –H-vibration bonds are to be found in the IR-spectrum.

The fibres have changed to partially condensated silanol-fibres, which are stable over a time period of several months.

Claims

1. Biologically degradable and/or biologically resorbable fibres, which are obtainable by drawing fibres from a spinning mass and their eventual drying, whereby the spinning mass contains one or more partially or completely hydrolytically condensated compounds of silica, which derive by hydrolytic condensation from monomers of the general formula I

SiX_4 (I),

in which rests X are the same or different and stand for hydroxy, hydrogen, halogen, amino, alkoxy, acyloxy, alkyl carbonyl or alkoxy carbonyl and derive from alkyl rests, which are eventually substituted straight-chain, branched or cyclic rests having 1 to 20 carbon atoms, preferably having 1 to 10 carbon atoms and can be interrupted through oxygen or sulphur atoms or through amino groups.

2. Method for preparation of biologically degradable and/or biologically resorbable (continuous) fibres having a flat fibre surface according to claim 1, the method comprising the following characteristic features:
   - preparing a spinning mass by hydrolytic (partial) condensation of one or more Si-compounds of the general formula I and/or precondensates derived therefrom defined in claim 1,
   - performing the hydrolytic condensation, eventually in the presence of a catalyst and/or a solvent by adding water by
   - using such a big amount of water, that the molar ratio $SiX_4 : H_2O$ is between 1 : 1 and 1 : 10, preferably between 1 : 1.5 and 1 : 2.5,
   - using a phase-transfer catalysator or such a big amount of water-soluble solvent (S) or mixture of solvent, that the molar ratio is $S : SiX_4 \geq 1$, preferably > 1,
   - removing S after the terminated hydrolysis and adjustment of a dynamic balance until the resulting mixture has in room temperature and in shear rate of 20 s^{-1} a viscosity between 0,05 and 50 Pa·s, preferably between 0,5 and 2 Pa·s,
   - exposing the resulting mixture to filtration after removing the solvent,

- allowing the resulting mixture to stand after filtration until it obtains spinnability,
- drawing threads from the spinning mass and eventual drying thereof.

3. Use of fibres according to claim 1 as biologically degradable and /or biologically resorbable reinforcement fibres.

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(57) Abstract

The present invention is concerned with controllably dissolvable silica-xerogels prepared via sol-gel process and their use. Specifically, the invention is concerned with a delivery device comprising controllably dissolvable silica-xerogel into which structure a biologically active agent is incorporated. The invention is further concerned with pharmaceutical preparations comprising said delivery device. Further, the invention is directed to medical devices for orthopedic and surgical purposes comprising controllably dissolvable silica-xerogels, which may further comprise a biologically active agent.

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DISSOLVABLE OXIDES FOR BIOLOGICAL APPLICATIONS

TECHNICAL FIELD OF THE INVENTION

The present invention is directed to controllably dissolvable sol-gel produced silica-xerogel materials and their use. Specifically, the present invention is directed to controllably dissolvable silica-xerogel particles of small diameter, prepared via sol-gel process where the gelation of the sol and evaporation of the solvent occur simultaneously. More specifically, the invention is directed to controllably dissolvable silica-xerogel particles of small diameter, prepared via sol-gel process where the gelation of the sol and evaporation of the solvent occur by a spray drying method or by a fiber spinning or drawing technique. Further, the invention is directed to controllably dissolvable sol-gel produced silica-xerogels as sustained and/or controlled release delivery devices for biologically active agents, especially medicines, proteins, or hormones, and to pharmaceutical preparations comprising said devices. Further, the invention is directed to implantable and transmucosal forms of said devices. And further, the invention is directed to implantable medical devices comprising controllably dissolvable sol-gel produced silica-xerogels, which may further comprise a biologically active agent.

BACKGROUND OF THE INVENTION

Silica-xerogels are partially hydrolyzed oxides of silicium. Hydrolyzed oxide gels can be produced by a sol-gel process, which has been used for producing ceramic and glass materials for many years.

The sol-gel process is based on hydrolyzation of a metal-alkoxide and subsequent polymerization of the metal hydroxides as follows:

1) $Si(OR)_4 + H_2O \rightarrow HO\text{-}Si(OR)_3 + ROH$

2) $HO\text{-}Si(OR)_3 + 3\,H_2O + ROH \rightarrow Si(OH)_4 + 4ROH$

3) $Si(OH)_4 + Si(OH)_4 \rightarrow (HO)_3Si\text{-}O\text{-}Si(OH)_3 + H_2O$

When the polymerization reaction goes further, additional chains, rings, and three dimensional networks are formed, and a gel comprising water, the alcohol of the alkoxy group and the gel itself is formed. The sol may also contain other additives such as acids or bases used for catalysis of the reaction. If alcohol and water are now extracted from the gel by washing and evaporating, a xerogel is obtained.

During drying large shrinking occurs creating internal stresses into the gel. If the monolithic gel is not allowed sufficiently time to relax its internal stresses, it will crack. During drying further polymerization of the remaining OH-groups occurs. The continuing polymerization carries on for a long time after gelation. This is called aging. The further the polymerization goes on, the more stable the gel or xerogel becomes. However, at room temperature the polymerization will effectively stop after a few weeks aging and the xerogel will not become totally inert. If the temperature is raised, the polymerization reaction can be accelerated, further stabilization and shrinkage occurs, and more internal stresses are introduced into the xerogel.

If the temperature is raised high enough (around 1000°C for monolithic Si-gels) the gel or xerogel becomes a pure oxide and there are no OH-groups present in the material. However, in case of pure oxides, the reaction rate is extremely slow. If the oxides are incorporated with other ions, such as Na, K, Mg, or Ca, the reaction rate can be greatly increased. The so called bioactive glasses are developed from these systems. The dissolution rate of these glasses is controlled by the composition and surface area of the glass. These glasses are melted above 1000°C.

The general principles of mixing organic substances with gels are well known. The basic idea is that an organic substance is added to the sol-stage of the sol-gel process. Then, after gelation, the organic part has become an inherent part of the material. In conventional glass melting processes, this is not possible at all because the temperatures are much too high for organic substances to survive.

The sintering temperature is naturally a limiting factor also for many substances in organically modified silicates (ORMOSILS). In the case of medicines, the sintering temperature is limited by the breakdown of the structure or functionality of the medicine. For proteins, enzymes, antibodies

and whole cells, the sintering limit is as low as 40°C since they will begin coagulating at and above that temperature.

Organic substances are generally added to silica gels to modify the natural properties of the silicates with those of the organic substances. Some combinations of dopants and matrices used thusfar are disclosed in Chemistry of Materials (1994) 6:1605-1614 (D. Avnir et al.).

Silicium sol-gel material directed for oral short term (less than 24 hours) drug delivery and methods of mixing drugs with silica-viscous sol have been described in Drug Development and Industrial Pharmacy (1983) 9 (1&2):69-91 (K. Unger et.al). The article describes a polycondensation in solution method, which starts with mixing polyethoxysiloxane (PES) with a solution of the drug in an appropriate solvent, giving a molecular scale entrapment of the drug in the polymer. The release rate of the drug is controlled by diffusion through the pores of the matrix material.

Published application EP 0680753 describes a sol-gel produced silica coating and particles containing a biologically active substance where the release rate of the active agent is controlled by addition of penetration agents, such as polyethylene glycol or sorbitol.

Published application WO 96/03117 discusses bone bioactive controlled release carriers comprising silica-based glass providing for the controlled release of biologically active molecules, their methods of preparation and methods of use. These carriers are stated to be prepared using a sol-gel-derived process.

SUMMARY OF THE INVENTION

An object of the present invention is to provide controllably dissolvable silica-xerogels prepared via a sol-gel process. A further object of the invention is to provide controllably dissolvable silica-xerogel particles of small diameter prepared via sol-gel process, where the gelation of the sol and evaporation of the solvent occur simultaneously. Specifically, the present invention provides controllably dissolvable silica-xerogel particles of small diameter prepared via sol-gel process, where the gelation of the sol and evaporation of the solvent occur by a spray drying method or by a fiber spinning or drawing technique.

A further object of the invention is to provide sustained and/or controlled release delivery devices for biologically active agents, especially medicines, proteins, or hormones, which are made of controllably dissolvable sol-gel produced silica-xerogel, and pharmaceutical preparations comprising said devices. Specifically, the present invention provides sustained and/or controlled release delivery devices for biologically active agents, which are made of controllably dissolvable silica-xerogel particles of small diameter prepared via sol-gel process, where the gelation of the sol and evaporation of the solvent occur simultaneously, and pharmaceutical preparations comprising said devices.

A further object of the present invention is to provide a method of administering a biologically active agent to a human or animal body, which comprises implanting, injecting, or transmucosally attaching to a human or animal body a delivery device made of a sol-gel produced, controllably dissolvable silica-xerogel according to the present invention, in which structure a biologically active agent is incorporated.

A further object of the present invention is to provide an implantable medical device comprising controllably dissolvable sol-gel-produced silica-xerogel, which may further comprise a biologically active agent.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows graphically the percentage of the remaining silica-xerogel implant and ^{3}H-toremifene activity at different time points of the *in vivo* experiment of Example 5.

DISCRIPTION OF THE INVENTION

Applicants have discovered that silica-xerogels prepared via a sol-gel process, and silica-xerogel particles of small diameter prepared via sol-gel process where the gelation of the sol and evaporation of the solvent occur simultaneously, dissolve controllably for a long (more that 24 hours) period of time. Further, the biologically active agents incorporated into the silica-xerogel structure are also released controllably for a long period of time. Therefore, the silica-xerogels of the invention can be used for a long-term delivery of biologically active agents. Thus, they can be used for delivery devices or pharmaceutical preparations that are, for example,

implanted or injected into, or transmucosally attached to a human or animal body. Administration into any tissue, soft tissues or bone, is possible. This allows local application so that targeting of the biologically active agent release site is possible. Therefore, the maximum effect from the agent is received.

A delivery device or a pharmaceutical preparation is implantable subcutaneously; intramuscularly; intraosseously; in oral, sinuidal, and uteral cavities; and into any diseased tissue. Transmucosally attached delivery devices or pharmaceutical preparations can be, e.g., particles, such as spheres, administered as a spray into sinuidal or lung tissue where they will dissolve and release the biologically active agent. Similarly, small particles can be injected in a carrier fluid in the tissues.

It has also been found that the silica-xerogels of the invention can be used for implantable medical devices. A medical device of the invention can be implanted into any human or animal tissue. Silica-xerogels of the invention dissolve totally during the period desired when they are in contact with body fluids. Thus, delivery devices and medical devices of the invention dissolve totally and controllably.

In this connection, a delivery device is a silica-xerogel incorporated with a biologically active agent into the structure. A pharmaceutical preparation, such as a granulate or capsule, in this context is a preparation that comprises the delivery device and possibly additional excipients useful in pharmaceutical preparations. A medical device of the invention is also useful for orthopedic and surgical purposes and need not contain a biologically active agent incorporated into the structure of the silica-xerogel. A medical device may be, e.g., a woven or nonwoven mat made of silica-xerogel fibers.

The silica-xerogel material of the invention has been found to be very biocompatible. In other words, it does not adversely affect the surrounding tissue, e.g., by causing an inflammation reaction.

The silica-xerogel of the invention dissolves controllably, and the release of the biologically active agent from the silica-xerogel of the invention is based on this dissolution, which allows constant local release of the biologically active agent into the tissue. The release rate of the biologically active agent can be controlled via processing parameters of the

gelation conditions such as spray drying temperature. Also factors such as the surface area/volume ratio of the material, the elemental composition of the silica-xerogel, and the dimension of the gel, which allows faultless silica-xerogels to be produced, control the release rate of the biologically active agent.

The silica xerogel matrix and the incorporated biologically active agent are released slowly when diameter of the xerogel particles is in the order of about 1- 500 µm. When the diameter of the particles is increased, the release rates of the matrix and the active agent are also increased.

The biologically active agent can be any organic or inorganic agent that is biologically active. The biologically active agent can be, e.g., a medicine, a protein, a hormone, a living or dead cell, a bacteria, a virus or a part thereof. Biologically active agents include those especially useful for long-term therapy, such as hormonal treatment, e.g., contraception and hormone replacement therapy and for the treatment of osteoporosis, cancer, epilepsy, Parkinson's disease, pain, and cognitive dysfunction. The suitable biologically active agents may be, e.g., anti-inflammatory agents, anti-infectives (e.g., antibiotics and antiviral agents, such as glindamycin, miconazole), analgesics and analgesic combinations, antiasthmatic agents, anticonvulsants (e.g., oxycarbazepine), antidepressants, antidiabetic agents, antineoplastics, anticancer agents (e.g., toremifene, tamoxifene, taxol), antipsychotics, antispasmodics, anticholinergics, sympatomimetics, cardiovascular preparations, antiarrythmics, antihypertensives, diuretics, vasodilators, CNS (central nervous system) drugs such as antiparkinsonism dugs (e.g., selegiline), steroidal hormones (e.g., estradiol, progesterone, nestorone), sedatives (e.g. atipamezole, dexmedetomidine, levomedetomidine), tranquilizers, and cognitive dysfunction drugs. The medicine can be in the form of a salt, such as selegiline hydrochloride, (-)-4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride, 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride, dexmedetomidine hydrochloride and toremifene citrate. The medicine can also be in the form of a free acid, such as ibuprofen; a free base, such as coffein or miconatzole; or a neutral compound, such as Z-2-(4-(4-chloro-1,2-diphenyl-but-1-enyl)phenoxy) ethanol. A peptide can be e.g. levodopa, and a protein can be e.g., an enamel matrix derivative or a bone morphogenetic protein. An effective amount of a biologically active agent can be added to the reaction mixture at any stage of the process. However,

it is preferable to add the biologically active agent to the reaction mixture at the sol-stage before polycondensation reaction takes place or mix it with the starting materials. The precise amount employed in a particular situation is dependent upon numerous factors, such as the method of administration, type of mammal, the condition for which the biologically active agent is administered, the particular biologically active agent used, the desired duration of use, etc. The amount of toremifene citrate in the silica-xerogel may vary from about 1 w-% to about 40 w-%.

The controllably dissolvable silica-xerogels of the invention can be prepared by allowing silica-alkoxide, such as tetraethylorthosilicate (TEOS), to react with water and optionally a solvent, e.g. ethanol or polyethylene glycol, or a combination of solvents, at low temperature, such as -20 °C to 100 °C, preferably at room temperature, in the presence of an acidic, e.g. acetic acid, or a basic catalyst by hydrolyzation (sol is formed) and polycondensation (gel is formed). The catalyst should be chosen not harming the biologically active agent.

In contrast to the production of monolithic silica-xerogels and silica coatings, in producing silica-xerogel particles of small diameter, for example by a spray drying method or a fiber spinning or drawing method, the gelation of the sol and evaporation of the solvent occur simultaneously, forming controllably dissolvable particles of small diameter, such as spheres or fibers. When the gelation is allowed to be completed before evaporation of the solvent, the formed gel is a monolith extending from wall to wall of the container. In contrast, in the present invention where the gelation of the sol and evaporation of the solvent occur simultaneously, for example by a spray drying method or a fiber spinning or drawing method, the evaporation of the solvent from the sol forces the colloidal nano-sized gel particles already formed close to each other and forces them to react with each other thereby leading to the formation of silica-xerogel particles.

In the present invention, it has been shown that when the gel is produced in particles of small diameter, such as spheres and fibers, internal stresses of the gel formed during drying are avoided almost completely and the particles are slowly degradable.

Thus, slow release materials may now be produced at low temperatures without necessarily having to sinter at all, allowing for use of all organic substances as ingredients.

Dried and/or partially sintered gels, i.e., xerogels, comprise SiO_2 modified with OH-groups that break the continuous silica network. In order for these oxides to dissolve, hydrolyzation of the bonding between an oxygen atom and a metal atom must be broken, and a hydrogen atom takes the place of the metal. Thus, the metal oxide network becomes discontinuous. The hydrolyzation can advance all the way, breaking all metal to metal oxygen bonds untill the oxide has totally dissolved.The dissolution behaviour of xerogels depends on several parameters.The sintering or drying temperature is a parameter, which has an influence on the dissolution rate of the material. An increased sintering temperature increases the polycondensation reaction rate and final state. Other parameters that control the polycondensation reaction, such as TEOS:H_2O molar ratio, pH of the silica sol, aging, gelation rate, shape, i.e., thickness of the gel, and, drying, have a minor influence on dissolution behaviour of gels sintered at low temperature (below 300°C). Further, different additives, such as polyethylene glycol or sorbitol which are used as penetration agents, have also only a minor effect on the release rate of the bioactive agent. The composition of the gel also has an influence on the dissolution behaviour, especially on materials sintered at above 200°C. The composition of the xerogel can be altered with elements such as Na,Ca, P, K, Mg, Cl, Al, B, Ti, N, Fe, and C.

Porosity and surface area of the silica-xerogel can be influenced by the sintering temperature and additives. When sintered at the same temperature, different additive compositions have a large influence to the porosity and surface area. However, this change has only a minor influence to the dissolution rate of the xerogels produced near room temperature. The dissolution rates of xerogels produced at high temperatures (500-1100°C) will be influenced stronly by these factors.

Instead, the diameter of the single gel-object and the production method seem to have a profound influence on the dissolution rate of the xerogel. Particles of silica gel may be produced in different ways. The traditional crushing results in particles that dissolve at the same rate as the bulk material per unit surface area. In WO 9603117, the release of vancomycin from crushed silica xerogel particles of 500-700 µm is decribed. The release was very rapid and most of incorporated vancomycin (about 90%) released during the first day. In contrast, if for example the sol is spray dried into particles (below 200 µm) at room temperature and kept in

an exciccator for 2 months, dissolution of incorporated drug wil be constant and total dissolution will last for 6 days. The dissolution rate of the spray dried particles seems to be over six times slower than the dissolution rate of the crushed particles *in vitro*.

In the present invention, silica gel particles and spheres are produced by spray drying above the melting point of the silica sol. During spraying into air, the small droplets dry in the atmosphere sufficiently to result in gelation of the hydrolized silica ions and colloidal gel particles. If the droplets hit a surface before sufficient drying, they will form pseudo-spheres caused by surface energy differences between the droplet and the substrate. In that case, they will also gelate as pseudospheres. The gelated particles are heat treated or aged at room temperature which results in further polymerisation of the OH-groups. The heat or aging treatment slows the dissolution of the particles significantly. The particles can be incorporated with ions, such as Na, K, P, Ca, Mg, Al, and B, in order to produce dissolvable and/or bioactive bone bonding particles.

Spray drying of the gel particles without biologically active agent at the room temperature and aging them in an exciccator gives homogeneous, faultless particles with slow dissolution. These particles dissolve linearly at a rate of 1.9 w-% per week. From the at the room temperature spray dried particles with biologically active agent, silica released linearly at the rate of 22.4 w-% per week. Microspheres (< 50μm) containing 10 w-% biologically active agent, prepared by mini spray dryer (Buchi, Switzerland) at 132°C, dissolved at a rate of 77.3 w-% per week. Without a biologically active agent the release rate of 5.8 w-% per week was measured.

Controllably dissolvable silica-xerogel fibers can be produced by sol-spinning technique withfurther aging or treating with low temperature heat. The production temperature can be kept near room temperature. The fiber production techniques give homogeneous and faultless materials. Silica-xerogel fibers produced by a glass rod spinneret technique and kept in an exciccator for four months produced materials that dissolved 2.5 w-% per week. The fibres can be incorporated with ions, such as Na, K, P, Ca, Mg, Al, and B, in order to produce dissolvable and/or bioactive bone bonding fibers.

Vowen or nonvowen mats prepared from silica-xerogel fibers of the invention can be used to separate two or more types of tissues from each other. They can also be used as bone repair mats. It is advantageous if the tissue guide is dissolvable so that it does not need to be removed by second operation. The non-sintered and aged fibers of the invention were found to exhibit dissolution rates acceptable for such applications (10 w-% in 4 weeks).

A bone collecting filter is a medical device placed on a suction tube, which removes the debris and excess liquids from the operation site. When the surgeon is drilling, sawing, grinding or otherwise working on bony tissue the bone chips can be collected with the filter and placed back into the defect. So far, these filters are not dissolvable in the tissue. If these filters were made of sol-gel produced fibers or particles, they could be made dissolvable and loaded with a biologically active agent. Thus, the entire filter could be placed into the defect site with the bone chips.

The implants made of silica-xerogel fibermats are flexible and dissolvable.

Polylactic acid, polyglycolic acid and polykaprolacton are degradable polymers used in medical devices which, however, need to be reinforced to achieve and maintain sufficient strength long enough while the degradation reduces the strength of the matrix. Controllably dissolvable silica xerogel fibers and particles of the invention are ideal for this purpose since they have the sufficient strength and a controllable dissolution rate. They may also be used for strengthening plastic packing materials which may be made of polylactic acid, starch or any other biodegradable polymer.

Sol-gel produced controllably dissolvable silica-xerogels according to the invention can be used as cell growth substrates in the form of for example, membranes and coatings made from spray dried particles or fibers. Cell growth assisting substances are released from the substrate with the dissolving silica.

The following examples are intended to illustrate the invention, and are not to be construed as being limitations thereon.

EXAMPLE 1
Production of silica-xerogel monolith

A sol for the monolithic siliga gel was prepared from TEOS, distilled water and CH_3COOH in 1/14.2/0.5 ratio. Polyethylene glycol was used as an additive in a 0, 0.005 (average molecular weight of 10,000), or 0.012 (average molecular weight of 4,600) ratio.

Silica-xerogels were prepared by the hydrolysis and polycondensation of TEOS with or without polyethylene glycol and water at room temperature. A small amount of a catalyst (acetic acid) was added to accelerate the reaction. Drug crystals were added to clear hydrolyzed solution, and silica sol was casted into wells of microtiter plate kept at 40°C in an oven for hydrolysis, polycondensation and aging for 18 hours. The aged silica gels were soaked in water for two days to leach out residual organic within the gel and dehydrated at 40°C to constant weight for a few days to obtain a silica-xerogel containing incorporated drug. A fraction of the silica xerogels were sintered at 80°C or 120°C (2°C/h, 2h at 80°C/120°C). Toremifene citrate was used as model drug in studies, which evaluated the effect of PEG, sintering temperature and drug content on the release rate of drug and silica from the matrix.

In vitro dissolution test

The dissolution profiles of toremifene citrate and silica from silica-xerogel were studied using the USP XXII dissolution apparatus II (paddle method, Sotax AT6, Basel, Switzerland) at constant temperature (37°C). Simulated body fluid (SBF, pH 7.4) containing 0.5% (m/v) sodium dodecyl sulphate was used as dissolution medium. SBF was prepared by dissolving reagent grade NaCl (136.8 mM), $NaHCO_3$ (4.2 mM), KCl (3.0 mM), $K_2HPO_4x3H_2O$ (1.0 mM), $MgCl_2x6H_2O$ (1.5 mM), $CaCl_2x\ 2H_2O$ (2.5 mM) and Na_2SO_4 (0.5 mM) in distilled water. They were buffered at pH 7.4 with tris-(hydroxymethyl)aminomethane (50 mM) and hydrochloric acid.

The volume of dissolution medium was 250 ml. Agitation intensity was 50 rpm and temperature was 37°C.

The absorbance values of the dissolution samples were measured on an UV-visible spectrophotometer (Hewlett Packard 845/A, USA) at maximum absorbance of toremifene citrate (A_{278}). Dissolved silica was

measured spectrophotometrically as a silica-molybdenblue complex at A_{820} (Koch and Koch-Dedic, 1974).

Porosity

The porosity of the silica xerogel samples was measured using the high pressure porosimeter (autoscan 33, Quantachrome Corp. U.S.A.). Pore diameters of 6.5 nm -14 µm were measured.

Results

Toremifene citrate was added as crystal particles into reaction mixture, and it appeared as a molecular dispersion in silica gel matrix. The concentration of added toremifene citrate in silica sol varied between 1.9-5.5 wt-% (corresponding to about 11.5-34.4 wt-% of drug in the air dried gel). Higher amounts of toremifene citrate precipitated during gelation at 40°C.

The effect of the drug content was studied on sintered silica gels (120°C) containing 11.5, 22.9 and 34.4 wt-% of toremifene citrate. The release profile of toremifene citrate was linear according to zero-order release kinetics. The release of toremifene citrate was slowest from silica-xerogel containing 11.5 wt-% drug (0.05%/mg implant/h) and fastest from silica xerogel with 34.4 wt-% drug (0.11 %/mg implant/h).The silica matrix dissolved according to zero-order release.

The sintering of silica-xerogels at temperature ranges used did not show any significant effect on the release rate of toremifene citrate or silica.

Unger et al. indicate that water soluble polymers such as polyethylene oxides enhance the liberation of medicines from polycondensed silica gels. However, the release of toremifene citrate or silica from silica-xerogel cylinders was not enhanced by the added polyethylene glycol. Actually, toremifene citrate and silica release was fastest from silica-xerogels without polyethylene glycol. Toremifene citrate released linearly at the rate of 0.16 %/mg implant/h and silica 0.31 %/mg implant/h. From silica xerogels containing PEG 4600, toremifene citrate released linearly at the rate of 0.13 %/mg implant/h and from xerogels containing PEG 10 000, 0.1 %/mg implant/h. Also dissolution of silica was fastest from silica xerogel without PEG, 0.31 %/mg implant/h. From xerogels containing PEG 4600, silica released linearly at the rate of 0.24 %/mg

implant/h and from xerogels with PEG 10 000 at the rate of 0.16 %/mg implant/h.

A correlation between silica and toremifene citrate release was found, meaning that the release of toremifene citrate was mainly controlled by dissolution of the silica-xerogel matrix (r_{mean} = 0.995).

Addition of PEG seems to decrease the total pore volume and surface area of pores especially in the 120°C sintered samples. In earlier study water soluble polymers were used in the sol-gel process to control the pore size distribution (Sato et al., J. Mat. Sci. 25, 4880-85, 1990). In the study, PEG decreased the surface area and decreased the pore size.

Table 1.
Porosity parameters of the silica xerogel samples (n=2)

SAMPLE	TOTAL PORE VOLUME (ml/g)	SURFACE AREA OF PORES (m^2/g)	MEAN PORE SIZE (nm)	MEDIAN PORE SIZE (nm)
PEG 4,600 120°C (n=1)	0.050	16.47	12.2	11.8
no PEG 120°C (n=2)	0.069 (0.001)	22.01 (2.025)	12.3 (0.5)	12.0 (0.8)
PEG 10,000 120°C (n=2)	0.042 (0.001)	13.65 (0.43)	12.4 (0.2)	12.0 (0.5)
PEG 4,600 40°C (n=2)	0.021 (0.001)	5.84 (0.80)	14.5 (1.1)	15.6 (1.3)
no PEG 40°C (n=2)	0.040 (0.007)	12.51 (3.01)	12.9 (1.1)	12.3 (1.4)
PEG 10,000 40°C (n=2)	0.038 (0.005)	10.92 (0.75)	13.9 (0.7)	13.2 (0.9)

Selegiline hydrochloride, (-)-4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride, dexmedetomidine hydrochloride, ibuprofen, and coffein can also be incorporated into silica sol prepared above. Peptides (levodopa) and proteins (an enamel matrix derivative) can also be incorporated into the above silica sol.

EXAMPLE 2
Production of silica xerogel fibers

A sol for the fiber drawing purpose was prepared from TEOS, distilled water, HNO_3, and ethanol in 1/2.0/0.036/1.0 ratio. The sol was allowed to form colloidal gel particles for 1 hour at 75 °C before drawing. Silica-xerogel fibers were prepared from the sol using a glass-rod spinneret

technique. The fibers were drawn in the spinneret reactor, where the polycondensation occurred at 75°C. The viscosity of the sol at the start of fiber drawing was found to be approximately 10 mPas. The fibers were put into aqueous solution within 48 hours and 4 months later. The fibers were also treated at 300°C and 700°C (heating rate 10°C/h, 2 h at max.T) in addition to the fibers kept at room temperature. The fibers were dissolved into a tris-methylaminomethane-HCl-buffered water or simulated bodyfluid (pH=7.54 , 23°C; pH=7.40, 37°C).

The silica, calcium and phosphate contents were analyzed from the solutions with atomic absorption spectroscopy; weigth loss of the fibers was measured; and SEM-EDX analysis was performed on the remaining fibers.

Results

The drawn fibers are smooth and, as-prepared, they are translucent. By light microscopy neither scattering nor cavities could be detected. The fibers were in amorphous state with respect to an x-ray diffraction pattern. Moreover, microcracking or flaw type failures could not be detected. The fiber surface drawn by glass-rod technique consists of small pores with diameters of about 100 nm. Only the fibers kept at room temperature (RT) dissolved at any significant amounts. The RT-fibers stored for 4 months in an excicator dissolved 10 w-% within 4 weeks.

The tensile strength of the as-prepared fibers was measured to be in the area up to 800 MPa for fibers of a diameter of about 10 µm. The Young's modulus of these fibres was measured to be in the area of 5 GPa. The strain-to-failure was above 10%, which is a typical value for glass fibers. The mechanical properties of the fibres are affected by the heat-treatment (drying) temperature.

Silica-xerogel fibers *in vivo*

In this experiment, sintered (200°C, 400°C, 600°C, and 800°C) and non-sintered silica-xerogel fibers were studied subcutaneously with rats. The fibers were sterilized with hot air, except the non-sintered fibers, which were sterilized in ethanol (70% for two hours, drying in an excicator for 2 days).

The animals were anesthesized with a solution of HYPNORM (phentanyl citrate 0.315 mg/ml and fluanisone 10 mg/ml) and DORMICUM

(midazolam maleate). The skin hair was removed. Two or three materials were implanted in the back subcutan of each animal. The animals were killed 2 weeks postoperatively. The tissue samples were embedded in PMMA, sectioned, ground and stained with toluidine blue or Von Kossa (5% silver nitrate solution, 0.1% safranine O solution and %5 sodium sulphate solution). The histological slices were analyzed light microscopically and scanning electron microspically.

Clinically, no swelling nor any signs of inflammation were observed. Wounds had healed well. In histological sections, no inflammatory reactions could be observed after two weeks postoperatively. Some slices contained macrophages in addition to fibroblasts, but the overall view appeared nonproblematic. In histological sections, toluidine blue stained the surroundings of the fibers blue, possibly because of the dissolved silica from the fibers. Almost all fibers had integrated well into the surrounding connective tissue. No signs of resorption of the fibers could be observed in SEM examination. No Ca,P-layer could be observed on the surface of the fibers. The inflammatory reaction caused by the fibers was negligible in rats.

EXAMPLE 3
Preparation of silica-xerogel fibers containing toremifene citrate

A sol for the fiber drawing purpose was prepared from TEOS, distilled water, HNO_3 and ethanol in 1/2.0/0.036/1.0 ratio. The sol was allowed to form colloidal gel particles at 75°C and toremifene citrate (400 mg/10ml) was dissolved in the sol after three hours. Before drawing the fibers by glass rod, the silica sol-gel was further allowed to form colloidal particles at 75°C for 8.5 hours.

EXAMPLE 4
Production of spherical spray dried silica xerogel particles at room temperature

TEOS, distilled water and acetic acid were mixed in 1:14.2:0.5 ratio at room temperature on a magnetic stirrer. After hydrolyzation, the sol was sprayed into air and the droplets were allowed to fall freely onto a polymeric substrate and gelate completely before collecting. The gelated particles were kept in an exciccator for four days before the dissolution test.

5,5 mg of gel particles (0,5-1000 µm) were placed in 50 ml of simulated body fluid (SBF) at 37°C and pH 7.4. The dissolution vessel was under gentle shaking movement during dissolution. Three parallel measurements were performed on each of the three parallel samples after 171, 336 and 504 hours. The particles dissolved 1.9 w-% within a week.

The spray dried particles (60-200 µm) containing toremifene citrate were prepared by the above method. Toremifene citrate at the concentration of 20 mg/ml was dissolved in silica sol for spray drying after 1 hour hydrolyzation.

Dissolution of the drug and silica from silica-xerogel particles containing 10.2 w-% toremifene citrate were studied as described in example 1 after two months from preparation. Toremifene citrate and silica released linearly from the particles. Toremifene citrate released at the rate of 0.68 w-% per hour and silica 0.13 w-% per hour.

EXAMPLE 5
Production of silica-xerogel discs containing toremifene

A sol for the monolithic silica-xerogel was prepared from tetraethoxysilane (TEOS, Aldrich), deionized water, acetic acid (CH_3COOH, J.T.Baker), and polyethylene glycol (PEG, Mw 4600, J.T.Baker) in a 1/14.2/0.5/0.0012 ratio at room temperature (RT). Toremifene citrate (33 mg/g) and ^3H-treated toremifene (16 µCi/g) were added to the solution. The solution was cast in blister-plate wells (100 µl/well) and kept at 40°C for hydrolysis, polycondensation, and aging for 18 hours. The aged silica-xerogel was dried at 40°C to constant weight.

Toremifene loaded silica-xerogels discs *in vivo*

Sixty female mice (C57B1, Denmark) with the average weight of about 19.6 g (SD 1.2) were studied. The animals were divided into two experimental groups (5 mice in each group): a toremifene treated silica-xerogel group and untreated silica-xerogel group. The animals were treated for 7, 14, 21, 28, 35, and 42 days. The ^3H-toremifene dose was about 80 µCi/kg (0.8 µCi/implant); toremifene citrate, 350 mg/kg (appr. 3.4 mg/implant); and silica gel, about 1.53 g/kg body weight. A toremifene loaded silica-xerogel disc was implanted subcutaneously an each side of the backbone.

After a predetermined period of time the silica-xerogel discs on the left side of the backbone were explanted together with the surrounding tissue, fixed in 70% ethanol, and embedde in Technovit (Algol). Sections of 20 µm were stained with toluidine blue. Samples of liver, kidney, and lymph node were fixed in buffered formaldehyde (Merck) and embedde in paraffin. Sections of 6 µm were stained with hematoxylin eosin. All tissue samples were evaluated using light microscopy. The silica-xerogel discs on the right side of the backbone were cut out from the surrounding fibrous capsule and dried at RT in a desicator for 24 hours. Their weights were determined and the precentage of implant remaining at each point was calculated.

To determine the amount of toremifene remaining in the implants, the dried discs were dissolved in 0.1 N NaOH and the activity was measured in a liquid scintillation counter (model 81000, LKB-Wallac, Turku, Finland). After sacrifice of the mice, the tissue samples taken from the application area were burned in an oxidizer (Junitek, Kaarina, Finland).

The weight loss of the silica-xerogel matrix was about 75 w-% during 42 days. The erosion rate was fast during 28 days and then decreased as seen from Figure 1. The silica-xerogel discs showed sustained release of toremifene during the test period. The amount of ^{3}H-toremifene remaining in the implant after 42 days was still about 16% (see Figure 1). The release rate of toremifene was controlled by the bioerosion of the silica-xerogel matrix. The correlation between silica and ^{3}H-toremifene release was r=0.9890.

The untreated silica-xerogel implant did not cause irritation at the implantation site. A fibrotic capsule formed around the implant.
No extensive silica-xerogel related systemic toxicity could be observed. The silica-xerogel gave sustained release for over six weeks. According to the above study, the silica-xerogels are biocompatible and controllably dissolvable. Thus, the silica-xerogel is a suitable carrier for a long term implantable delivery system.

EXAMPLE 6
Production of spherical spray dried silica-xerogel particles containing toremifene at pH 3.8 by mini spray dryer

A sol for spray drying purpose was prepared from TEOS, distilled water and acetic acid in 1:14.2:0.5 molar ratio at room temperature on a magnetic stirrer. After hydrolyzation toremifene citrate was dissolved (20 mg/ml) and the sol was spray dried by mini spray dryer (Buchi, Switzerland). The pH of the sol was 3.8 after addition of toremifene citrate. The spray drying conditions were following: inlet temperature 134°C, flow 600, aspirator 90, pump 16.

About 40-50 mg of gel particles (< 50 µm) were placed in 250 ml of simulated body fluid (SBF) at 37°C and pH 7.4. The dissolution profiles of toremifene citrate and silica were studied using the USP XXII dissolution apparatus II (paddle method, Sotax AT6, Basel, Switzerland).

The release profile of toremifene citrate was linear according to the square root of time kinetics. After 30 hours 80 w-% of toremifene citrate was released. The release of silica was linear. Silica microspheres dissolved at a rate of 0.46 w-% per hour.

EXAMPLE 7
Production of spherical spray dried silica-xerogel particles containing toremifene citrate at pH 2 by mini spray dryer: Effect of aging

The solution for spray drying purpose was prepared with a mole ratio of TEOS:H_2O:HCl = 1.0:14.2:0.003. Toremifene citrate was dissolved after one hour hydrolyzation at the concentration of 20 mg/ml. The pH of the sol with toremifene citrate was about 3.8. Before spray drying the pH of the sol was adjusted to pH 2.1 with hydrochloric acid. Silica sol was spray dried immedeately or after 65 hours aging at room temperature. The spray drying conditions were as described in Example 6. Dissolution of toremifene citrate and silica was performed as in Example 6.

The release of toremifene citrate and silica was according to square root of time kinetics (table 2). After 30 hours 63.1 w-% of toremifene citrate was released from the aged silica microspheres and 75.2 w-% from the unaged. The release of toremifene citrate was about 20% slower from aged microspheres. The release of silica from aged microspheres is about 20% slower than from unaged.

Table 2.
Release of toremifene citrate and silica from microspheres aged for 65h and without aging containing 11w-% toremifene citrate.

Toremifene citrate	aged for 65h (pH 2)	aged for 0h (pH 2)
slope (%/$h^{1/2}$)	9.79	12.2
correlation coefficient	0.9713	0.9888
cum released toremifene (%) after 30h	63.1	75.2
Silica		
slope (ug/$h^{1/2}$)	928.22	1047.47
correlation coefficient	0.9826	0.9898

EXAMPLE 8
Release of toremifene from crushed silica xerogel particles

A sol was prepared as described in Example 1 for monolithic silica-xerogel from TEOS, distilled water and acetic acid in a molar ratio 1:14.2:0.5. Polyethylene glycol (average molecular weight of 4.600) was used as an additive at a concentration 10 mg/ml. Toremifene citrate was dissolved in hydrolyzed sol at the concentration of 40 mg/ml. Silica sol was casted into test tubes kept at 40°C in an oven for hydrolysis, polycondensation and aging for 18h. Polymerized silica gel was crushed and dried to constant weight. Granules were in a size range of about 4-50 µm in diameter.

About 42 mg of gel particles were placed in 250 ml of simulated body fluid (SBF) at 37°C and pH 7.4. The dissolution profiles of toremifene citrate and silica were studied using the USP XXII dissolution apparatus II (paddle method, Sotax AT6, Basel, Switzerland).

Toremifene citrate dissolved linearly according square root of time kinetics at rate of 8.1%/$h^{1/2}$. Silica xerogel matrix dissolved linearily at a rate of 0.2 % per hour.

EXAMPLE 9

Production of silica xerogel monolith containing toremifene citrate: Effect of TEOS:H_2O ratio and water soluble polymers on dissolution of toremifene citrate and silica

Silica gels were prepared from TEOS, water, ethanol and HCl in the molar ratio 1:6:2.3:0.003 or 1:14:2.3 :0.003 at room temperature. Polyethylene glycol (average molecular weight of 10,000 or 4,600) was used as additive at the concentration of 10 mg/ml and toremifene citrate at the concentration of 20 mg/ml. Hydrolyzed sol was casted into wells of blister plate, kept at 40°C in an oven for hydrolysis, polycondensation and aging for 18 hours. The silica gels were dried at 25°C in a desiccator at 11% relative humidity to constant weight to obtain a silica xerogel containing incorporated toremifene citrate.

Dissolution profiles of toremifene citrate and silica were studied as in Example 1.

Release of toremifene citrate and degradation of silica matrix was studied at two different H_2O:TEOS molar ratios (14:1 and 6:1). Release of toremifene citrate was faster from silica matrix containing PEG with H_2O:TEOS ratio 6 than from matrix containing PEG with H_2O:TEOS ratio 14 (table 3). Without PEG the release rate was equal for both H_2O/TEOS ratios. Also degradation rate of the matrix containing PEG with H_2O/TEOS ratio 6 was faster (25-50%) than degradation of matrix with H_2O/TEOS ratio 14 (table 4).

Table 3.

Release of toremifene citrate from silica xerogels containing 1 w-% PEG of different molecular weight.

H_2O/TEOS = 14:1	PEG 4600	PEG 10000	without PEG
SLOPE %/mg IMPLANTxh	0.052	0.061	0.085
CORRELATION COEFFICIENT	0.9895	0.9902	0.9903
H_2O/TEOS = 6:1			
SLOPE	0.094 %/mgxh	0.922 %/mg IMPLANT $xh^{1/2}$	0.657 %/mg IMPLANT $xh^{1/2}$
CORRELATION COEFFICIENT	0.9773	0.9915	0.9909

Table 4.
Release of silica from silica xerogels containing 1 w-% PEG of different molecular weight.

H_2O/TEOS = 14:1	PEG 4600	PEG 10000	WITHOUT PEG
SLOPE %/mg IMPLANT xh	0.097	0.168	0.176
CORRELATION COEFFICIENT	0.9933	0.9896	0.9902
H2O/TEOS = 6:1			
SLOPE %/mg IMPLANT xh	0.188	0.221	0.181
CORRELATION COEFFICIENT	0.9896	0.9770	0.9743

EXAMPLE 10
Production of silica xerogel monolith containing toremifene citrate: Effect of aging and drying conditions

A sol was prepared as described in Example 1. Polyethylene glycol (Mw 4,600) was used as an additive (10mg /ml). Toremifene citrate was dissolved at the concentration of 20 mg/ml in the hydrolyzed sol after 1 hour. Sol was casted into wells of blister plate and kept at 40°C for 18 hours. Thereafter the gels were transferred to air tight test tubes for aging at 40°C for 7 or 28 days. Aged silica gels were dried to constant weight at 25°C at different relative humidities (11.4 %, 48.4% and 74.7%).

Dissolution of toremifene citrate and silica was studied as described in Example 1.

Silica dissolved linearly from all silica xerogel samples. Aging time did not affect the degradation rate of silica matrix (table 6). Toremifene citrate dissolved according to square root of time kinetics (table 5). Release of toremifene citrate was sligthly faster (about 30%) from 28 days aged silica xerogels than from unaged.

Table 5.

Dissolution of toremifene citrate from aged silica xerogels

AGING, DAYS	11.4 RH-%	48.4 RH-%	74.7 RH-%
0	r=0.9808 b= 0.46 %/mg implant /$h^{1/2}$	r=0.9924 b=0.53	r=0.9728 b=0.46
7	r=0.9869 b=0.59	r=0.9866 b=0.52	r=0.9943 b=0.06 %/mg implant/h
28	r=0.9974 b=0.67	r=0.9917 b=0.74	-

Table 6.

Dissolution of silica from aged silica xerogels

aging, days	11.4 RH-%	48.4 RH-%	74.7 RH-%
0 %/mg implant/h	r=0.9872 b= 0.17	r=0.9887 b=0.16	r=0.9729 b=0.2
7	r=0.9857 b=0.17	r=0.9907 b=0.17	r=0.9768 b=0.18
28	r=0.9898 b=0.16	r=0.9840 b=0.17	-

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the spesification and examples be considered as exemplary only.

CLAIMS

1. A controllably dissolvable silica-xerogel prepared via sol-gel process.

2. The controllably dissolvable silica-xerogel according to claim 1, wherein said process is such that gelation of the sol and evaporation of the solvent occur simultaneously, and where particles of small diameter are produced.

3. The controllably dissolvable silica xerogel according to claim 2, wherein the gelation of the sol and evaporation of the solvent occur by a spray drying method or by a fiber spinning or drawing technique.

4. A controllably dissolvable silica-xerogel particle of small diameter prepared via sol-gel process, where gelation of the sol and evaporation of the solvent occur simultaneously.

5. The controllably dissolvable silica-xerogel particle according to claim 4, wherein said particle is prepared by a spray drying method or by a fiber spinning or drawing technique.

6. The controllably dissolvable silica-xerogel particle according to claim 5, wherein said particle comprises a sphere or a fiber.

7. A delivery device comprising the controllably dissolvable silica-xerogel according to any one of claims 1-3, wherein said silica-xerogel contains a biologically active agent.

8. A delivery device comprising the controllably dissolvable silica-xerogel particle according to any one of claims 4-6, wherein said particle contains a biologically active agent.

9. The delivery device according to claim 7 or 8, wherein said biologically active agent is a medicine, a protein, a hormone, a living or dead cell, a bacteria, a virus or a part thereof.

10. The delivery device according to claim 9, wherein said biologically active agent is a medicine.

11. The delivery device according to claim 10, wherein said biologically active agent is toremifene or acid addition salt thereof.

12. The delivery device according to claim 11, wherein said biologically active agent is toremifene citrate.

13. The delivery device according to any one of claims 7-12, wherein said delivery device is implantable into a human or animal body.

14. The delivery device according to any one of claims 7-12, wherein said delivery device can be attached transmucosally or injected into a human or animal body.

15. A pharmaceutical preparation comprising a delivery device according to claim 7.

16. A pharmaceutical preparation comprising a delivery device according to claim 8.

17. An implantable medical device comprising a controllably dissolvable silica-xerogel particle of small diameter produced via a sol-gel process where the gelation of the sol and evaporation of the solvent occur simultaneously.

18. An implantable medical device according to claim 17, further comprising a biologically active agent.

19. A method of administering a biologically active agent into a human or animal body, wherein said method comprises implanting, injecting, or transmucosally attaching a delivery device, wherein said delivery device comprises a controllably dissolvable silica-xerogel, wherein said silica-xerogel, is produced by a sol-gel process, and wherein said silica-xerogel comprises a biologically active agent.

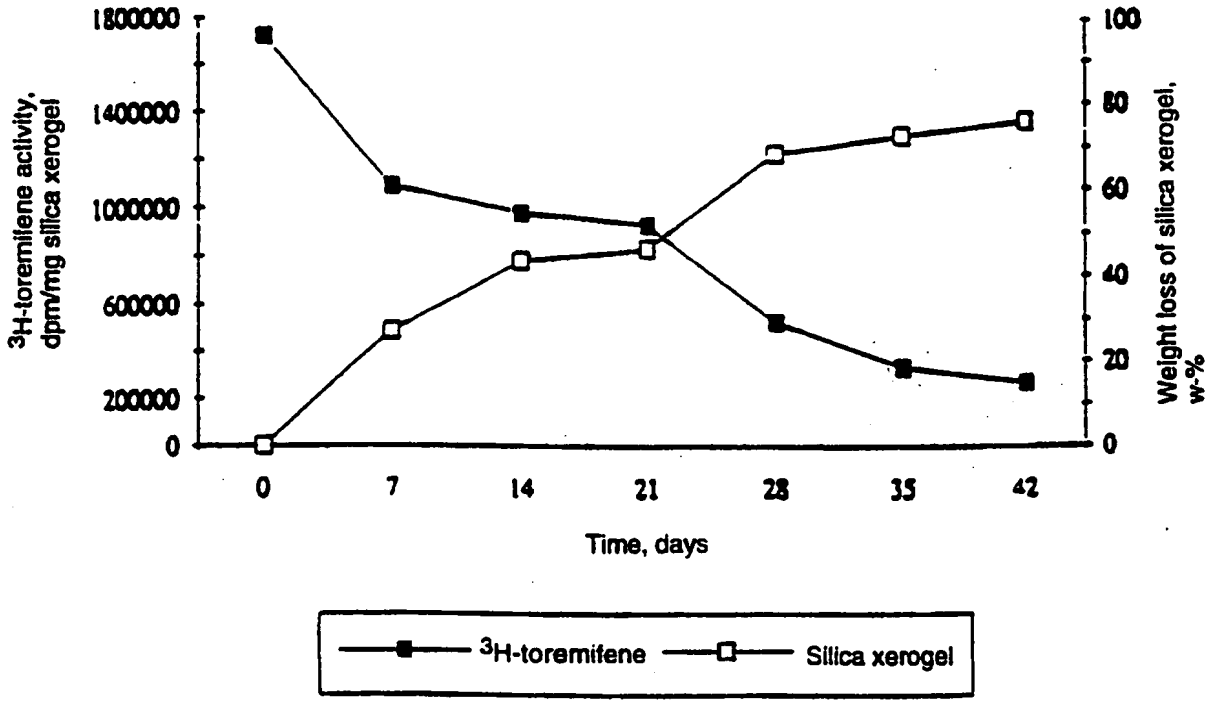
20. A method according to claim 19, wherein said silica-xerogel comprises a particle of small diameter prepared via sol-gel process where the gelation of the sol and evaporation of the solvent occur simultaneously.

21. A method of administering a biologically active agent into a human or animal body, wherein said method comprises implanting, injecting, or transmucosally attaching a delivery device, wherein said delivery device comprises a controllably dissolvable silica-xerogel, wherein said silica-xerogel, is prepared from tetraethoxysilane, and wherein said silica-xerogel comprises toremifene citrate.

22. A method according to claim 21, wherein said silica-xerogel comprises a particle of small diameter prepared via sol-gel process where the gelation of the sol and evaporation of the solvent occur simultaneously.

FIGURE 1

Percentage of the remaining silica-xerogel implant and ^{3}H-toremifene activity at different time points *in vivo*.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 97/00330

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C01B 33/16, A61K 47/02
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C01B, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG: WPI, CLAIMS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0336014 A1 (VECTORPHARMA INTERNATIONAL S.P.A.), 11 October 1989 (11.10.89), Example 1,5,6, --	1-18

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 August 1997	28-08-1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer May Hallne Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI97/00330

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19-22
because they relate to subject matter not required to be searched by this Authority, namely:

No international preliminary examination has been carried out on claims 19-22 because the subject matter of these claims is a method for treatment of the human or animal body by surgery or therapy. Rule 67.1 (iv).

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/08/97

International application No.

PCT/FI 97/00330

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0336014 A1	11/10/89	DE 3872382 A	30/07/92
		ES 2042700 T	16/12/93
		US 5008114 A	16/04/91

RELATED PROCEEDINGS APPENDIX

NONE